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*Cecil, R. A.: A Textbook of Medicine. Philadelphia, W. B. Saunders Co., 1947, p. 376.

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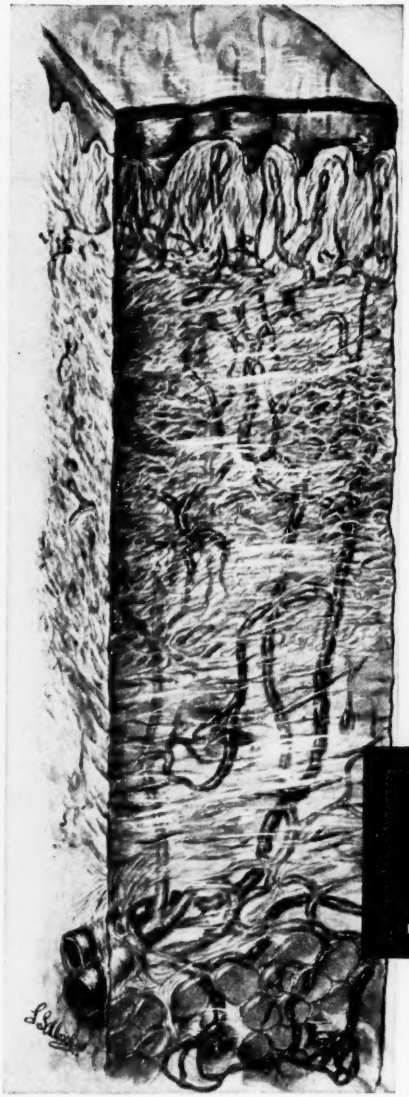

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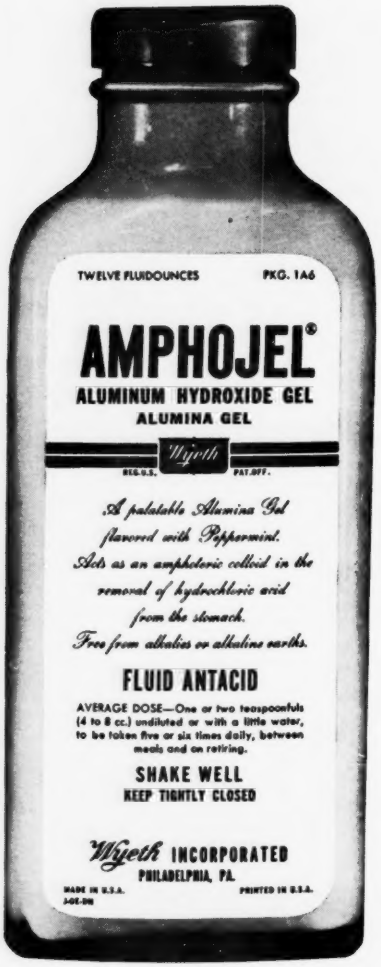
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RECRYSTALLIZED INSULIN FOR DIABETIC PATIENTS WITH INSULIN ALLERGY

J. ERIK JORPES, M.D.
STOCKHOLM, SWEDEN

ALLERGIC reactions from insulin can be viewed from different aspects. They cause difficulties in insulin therapy, sometimes even making a discontinuation of treatment with insulin compulsory. Of no less interest from a theoretic point of view is the question of the presence or absence of antigenic properties in insulin. As a hormone common to all vertebrate animals, insulin could be assumed to have a definite molecular structure irrespective of the species from which it derives and should not be antigenic. Nevertheless, authors who review the literature on this topic (Yasuna [1] and Watson [2]) tacitly accept the concept that insulin is an antigen, capable of inducing sensitization. Desensitization has consequently been considered as the last resort in cases of severe allergic reactions. Rapid (Corcoran,[3] Ulrich and others [4] and Bayer [5]) as well as prolonged (Weitz [6]) procedures for desensitization of the patients have consequently been worked out. If successful, the rapid desensitization eliminates the difficulties in the administration of insulin at least for a time. In Bayer's [5] case the effect lasted only for two weeks.

In a number of cases the same result can be achieved with much simpler measures, such as changing over to another brand of insulin or to an insulin derived from another animal species. This search for a suitable insulin becomes, however, less hopeful if the crystalline insulin, as is often the case, also gives untoward reactions.

From the Chemistry Department of the Caroline Institute.

1. Yasuna, E.: Generalized Allergic Reactions to Insulin: Review of Literature with Report of Case, J. Allergy **12**:295, 1941.

2. Watson, E. M.: Non-Hypoglycaemic (Allergic) Insulin Reactions, Canad. M. A. J. **47**:336, 1942.

3. Corcoran, A. C.: Note on Rapid Desensitization in Case of Hypersensitiveness to Insulin, Am. J. M. Sc. **196**:359, 1938.

4. Ulrich, H.; Hooker, S. B., and Smith, H. H.: Allergy to Insulin: Report of a Case, New England J. Med. **221**:522, 1939.

5. Bayer, L. M.: Desensitization to Insulin Allergy, J. A. M. A. **102**:1934 (June 9) 1934.

6. Weitz, M. A.: Insulin Hypersensitivity with Desensitization: Report of Case, J. Allergy **14**:220, 1943.

It is surprising to find how little stress is laid on the purity of the insulin. Being a protein, insulin can easily be contaminated with other proteins and their split products which are difficult to remove. Even with simpler compounds several recrystallizations are usually considered to be necessary for purification. With insulin, there is all the more reason to expect adhering impurities which can be removed only by repeated recrystallizations.

In almost all publications on insulin allergy the label "crystalline" has been taken as a guarantee of purity without any statements from the manufacturer concerning the procedure of purification. Not even in such essentially important papers as that of Wasserman, Broh-Kahn and Mirsky,[7] who immunized animals with insulin, were any statements made about the purity of the crystalline insulin used as antigen.

RELATION OF ALLERGIC REACTIONS TO PURITY OF THE INSULINS

In one of his earlier reports Lawrence [8] encountered allergic complications in 30 per cent of the insulin-treated patients. From the literature (Yasuna,[1] Hansen and Eyer [9]) one gets the impression that the local as well as the general allergic reactions following insulin injections were reduced in frequency with the introduction of highly purified commercial insulins. Altshuler [10] laid particular stress on the value of the crystalline insulin even in this respect. He found a disappearance of localized allergic reactions and of lipoatrophy on changing over to crystalline insulin. Ulrich and others stated (1939) that the reactions from crystalline insulin were less severe than those following the injection of standard insulin both in a case of their own and in those of several other authors (Baker,[11] Allan and Scherer [12] and Campbell, Gardiner and Scott [13]). They also quote Joslin,[14] who found 4 patients extraordinarily sensitive to the four regular American

7. Wasserman, P.; Broh-Kahn, R. H., and Mirsky, J. A.: Antigenic Property of Insulin, J. Immunol. **38**:213, 1940.

8. Lawrence, R. D.: Local Insulin Reactions, Lancet **1**:1125, 1925.

9. Hansen, K., and Eyer, H. D.: Klinische Studien über allergische Krankheiten; Insulin-Allergie, Arch. f. klin. Med. **174**:133, 1932.

10. Altshuler, S. S.: The Clinical Use of Crystalline Insulin, Ann. Int. Med. **11**:901, 1937.

11. Baker, T. W.: Clinical Survey of One Hundred and Eight Consecutive Cases of Diabetic Coma, Arch. Int. Med. **58**:373 (Sept.) 1936.

12. Allan, F. N., and Scherer, L. R.: Insulin Allergy, Endocrinology **16**:417, 1932.

13. Campbell, W. R.; Gardiner, W. J., and Scott, D. A.: Reactions After Administration of Crystalline Insulin, J. Clin. Investigation **9**:28, 1930.

14. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 5, Philadelphia, Lea & Febiger, 1935.

preparations of insulin but not to a crystalline form. The opposite findings of Corcoran,[3] Tuft[15] and Davidson[16] are not significant since no criteria of purity for the crystalline insulins were given. The same applies to the findings in animals of Wasserman, Broh-Kahn and Mirsky[7] and of Lowell,[17] who demonstrated antibodies for crystalline insulin in the serum of an allergic patient (Yasuna's patient). The antibodies reacted only with crystalline beef or pork insulin but not with insulin prepared from the human pancreas. The different behavior of the insulins was probably due to impurities. In accordance with this, Herzog[18] found that crystalline Bayer insulin gave a much stronger intradermal reaction than the crystalline insulin prepared by Novo, of Copenhagen.

The most definite statement about the nonantigenic nature of insulin was made by Hansen and Eyer[9] in 1933. They found a strong intradermal reaction in an allergic patient to seven different brands of insulin, a weak reaction to an insulin purified by coagulation in hydrochloric acid and no reaction at all to a once recrystallized British insulin (Wellcome). The material from the first crystallization, *"die Rohkrystalle,"* caused a weak but definite reaction, and there was none after recrystallization. They ascribed the antigenicity to *"verunreinigende Begleitkörper,"* or bodies accompanying the insulin which caused impurity.

The practical value of crystalline insulin as a therapeutic agent was clearly demonstrated by Feinblatt[19] in 1938. Eight patients who gave evidence of foreign protein reaction to protamine insulin therapy and 5 patients allergic to standard insulin were relieved of the allergic reactions under crystalline insulin therapy.

My own interest in this question dates back to 1941, when a colleague at the Serafimer Hospital in Stockholm (Malmström[20]) consulted me about a patient for whom he had not succeeded in finding

15. Tuft, L.: Insulin Hypersensitiveness: Immunologic Considerations and Case Reports, Am. J. M. Sc. **176**:707, 1928.

16. Davidson, M. T.: Insulin Allergy: Review of Recent Literature and Report of Case, J. Allergy **6**:71, 1934.

17. Lowell, F. C.: Evidence for Existence of Two Antibodies for Crystalline Insulin, Proc. Soc. Exper. Biol. & Med. **50**:167, 1942.

18. Herzog, K.: Beobachtungen über Insulin-Überempfindlichkeit und den Wert intracutaner Verträglichkeitsprüfungen für die Insulintherapie, Ztschr. f. klin. Med. **136**:297, 1939.

19. Feinblatt, H. M.: Crystalline Insulin Therapy: Absence of Foreign Protein Reaction, M. Rec. **148**:380, 1938.

20. Malmström, G.: Ett nytt insulinpreparat lämpligt vid fall av insulinöverkänslighet, Svenska läk.-tidning. **38**:2073, 1941.

any kind of insulin that did not give a reaction at the site of injection, despite trial of all the brands available. He described the case in question as follows:

A patient was suffering from fairly severe diabetes, necessitating insulin therapy. Considerable discomfort was experienced in the form of tender infiltrations, up to the size of a large orange, appearing at the site of injection approximately ten hours later and remaining for five to six hours. The patient complained of burning pains so intense as to disturb sleep at night. After injection in the legs the walking became difficult because of tension and pains. Two Danish preparations of insulin and a crystalline preparation of the insulin supplied by Organon (Holland) were tried as well as protamine zinc insulin and protamine insulin, but without improvement. There was, it is true, a variation in sensitivity with the various preparations, but all of them resulted in definite infiltrations and severe discomfort. Freedom from reaction was finally obtained with an ordinary insulin recrystallized four times, supplied by Vitrum, of Stockholm.

The insulin in question had been recrystallized four times by me to be used for chemical analysis. This observation was of great interest. It was evident that all the discomforts caused by the other brands of insulin were due to impurities.

Apart from the theoretic interest, the therapeutic possibilities in cases in which local or general reactions make treatment with insulin difficult or even impossible are worthy of attention. This principle was immediately adopted in Sweden. All patients who complained of severe local reactions following the injection of insulin received from the manufacturer, Vitrum, a usually three times recrystallized insulin. Some preparations were recrystallized five or seven times from a phosphate buffer solution, the mother liquor being carefully removed on a glass filter each time. Between 1942 and 1947 approximately 300 patients requested the purified insulin. The majority of them after a time no longer needed this insulin because of the disappearance of their hypersensitivity. Many of them, however, derived great benefit from it, and in certain cases it could not be dispensed with.

In the following pages I shall report on some typical cases that demonstrate how even serious hypersensitivity to insulin can regress spontaneously and on some which show that it can persist for years. Two patients who urgently needed the purified insulin are also described.

CASES OF PATIENTS WHO AFTER A TIME TOLERATED STANDARD INSULIN

CASE 1.—The patient was a woman aged 58 years. She was treated for diabetes in 1944, when infiltrations the size of the palm of a hand appeared after injection of insulin. She was therefore discharged from the hospital on diet only. She was hospitalized again for three weeks in November 1946. Despite the diet prescribed, she suffered from thirst and polyuria. Ordinary insulin and protamine zinc insulin (supplied by Vitrum), di-insulin (Novo, of Copenhagen) and "crystalline" insulin (Organon, of Holland) were tried. All caused infiltra-

tions the size of the palm of a hand. The patient could not continue with insulin therapy. An attempt was made at desensitization with dilutions of insulin, 1:1,000, and increasing doses. A dilution of 1:100, however, gave rise to infiltrations, and the experiment was discontinued. Since the diabetes was fairly mild and none of the usual commercial insulins was tolerated, she was discharged again on a fairly strict diet. Nevertheless she subsequently lost much weight and suffered from thirst and considerable polyuria. At the end of September 1947 a three times recrystallized insulin was tried. The patient tolerated this better. However, the dose necessary, 32 units daily, caused pain and itching at the site of injection. An infiltration about 1 inch (2.5 cm.) in diameter remained after twenty-four hours. If the patient received as small a dose as 8 units at one site, some subjective discomfort occurred, but there was no definite residual infiltration after twenty-four hours. The same dose (8 units) of the standard insulin caused an infiltration approximately 50 by 50 mm. and considerable subjective discomfort.

From November 1947 to February 1948 the patient used this three times recrystallized insulin at home. Her tolerance became successively improved, and finally no definite infiltrations were present but only a moderate burning sensation and pain for five to six hours after the injection. Gradually she became entirely free from discomfort following injection. When she was hospitalized on Jan. 22, 1948, for testing of some new insulins of varying degrees of purity, she was so satisfied with the previous preparation that she did not consider that she required any better one.

The surprising observation was now made that the patient tolerated even the ordinary commercial insulin. No definite infiltrations developed, and she did not consider that the burning pain and itching were particularly annoying. However, on visiting the outpatient department on Feb. 27, 1948, she stated that, despite the absence of infiltrations, she had such subjective discomfort that she would be grateful to receive one of the previously tested purified brands of insulin.

CASE 2.—The patient was a woman, aged 48 years, who had diabetes since 1940. During recent years she had suffered from eczema on the lower part of the legs, particularly the right one, which was more extensive since 1943. Since March 1944, thirst, considerable polyuria, cutaneous irritation, furuncles on the legs and eczema of the genitalia had been present. On March 21, she received two doses of insulin, of 40 and 20 units, which were not tolerated. Large infiltrations developed on the thighs and severe urticaria over the whole body. At the end of March 40 units of protamine insulin was given for two days but was not tolerated. Despite discomfort ordinary insulin was once more given until April 20. On that date two doses of 40 and 20 units of three times recrystallized insulin were given and tolerated. The patient was admitted to the hospital again on June 15. In the meantime she had tolerated the recrystallized insulin satisfactorily. During 1944 and 1945 she was hospitalized several times for control and for treatment of genitourinary disorders. After Aug. 25, 1945, the dose of insulin was increased to 44 and 24 units. During the whole time the patient received the recrystallized insulin, and during 1946 and 1947 she did not complain of any discomfort. She was able to carry out her household work. She was admitted to the hospital on Feb. 21, 1948, for testing of various brands of insulin. It was then found that she tolerated without discomfort three doses of 20 units each of two brands of insulin recrystallized several times as well as an amorphous insulin with 17 units per milligram. She continued to use ordinary commercial insulin.

CASE 3.—The patient was an elderly woman for whom diabetes was diagnosed in 1942. She was given ordinary insulin (Vitrum), but this gave rise to large local wheals at the site of injection. After about two months a change was made to insulin recrystallized three to five times, which has been used continuously since then by the patient without discomfort. Her hypersensitivity disappeared in the course of time, so that in March 1948 she tolerated the usual dose, 32 units every twenty-four hours, of an insulin containing only 16 units per milligram.

CASES IN WHICH RECRYSTALLIZED INSULIN WAS REQUIRED FOR A LONG PERIOD

CASE 4.—A man aged 61 years had mild diabetes since 1943. Owing to certain nervous disorders, including irritability, he found it difficult to maintain a diet, and insulin was therefore prescribed on March 19, 1947, beginning with protamine zinc insulin. After a few injections, local infiltrations occurred, and administration of insulin was therefore discontinued on April 10. On April 12 ordinary insulin was tried and was tolerated better. On June 13 protamine zinc insulin was once more given. This was tolerated at first, but troublesome infiltrations soon started. On a few subsequent occasions the patient himself made new but unsuccessful trials with ordinary insulin and protamine zinc insulin. He later received a specially purified insulin which he tolerated. As difficulties had arisen in connection with insulin therapy since March 1947, tests were made in March and April 1948 with an insulin recrystallized seven times, one recrystallized once and two amorphous preparations of insulin of which one contained 21 units and the other only 16 units per milligram. In addition he received protamine zinc insulin prepared from insulin recrystallized seven times. The two first mentioned, i. e., the recrystallized preparations of insulin, were each given for ten days in doses of 20 units every twenty-four hours. The patient stated that he had slight symptoms after injections in the right thigh and no swelling or redness after injection at other sites.

The last-mentioned preparations, i. e., the amorphous insulin, both caused "hard, tender swellings with considerable redness and itching lasting for several days." They could be used only for three days each.

Protamine zinc insulin prepared from insulin recrystallized seven times was tolerated in the same dose without local reactions.

This case is illuminating. As long as one year after the institution of insulin therapy, hypersensitivity was so pronounced that it was impossible to use ordinary insulin. When the patient was given four brands of insulin unknown to him and marked only with figures on the bottles, he stated that he suffered no noticeable discomfort after the two recrystallized preparations but severe discomfort after the amorphous preparations of insulin. All subjective errors of judgment must be excluded here, since the patient was unaware of the respective degrees of purity. It is evident that patients such as this one are in urgent need of recrystallized insulin for a considerable time, even for a year as in this case.

From one hospital, where such cases have been studied closely, the following more interesting cases are reported, in addition to 5 ordinary cases in which local reactions disappeared as soon as recrystallized insulin was prescribed.

CASE 5.—A man aged 44 years had diabetes since 1945. Edema followed the use of ordinary insulin. He received purified insulin on April 19, 1946, but complained that he still experienced a local reaction about once a week. On August

20 he was given, at his own request, a purer preparation, recrystallized three times, which he tolerated. On attempts to alternate with an amorphous insulin, 22 units per milligram, definite infiltrations occurred. The patient continued to use purified insulin recrystallized three times and is still using it.

CASE 6.—A woman aged 67 years had diabetes since about 1930. She had been taking insulin since October 1941. Itching over the entire body was present at the end of November 1941, and she was rehospitalized on December 4. Her nights were disturbed owing to prickling sensations and itching. After receiving purified insulin recrystallized four times the itching disappeared. Without the patient's knowledge ordinary insulin was once again administered. The discomforts reappeared, and it was necessary to resume administration of the purified insulin, which she has been using since then.

CASE 7.—The patient was a girl aged 11. Diabetes was diagnosed in 1944, and insulin therapy was started on Sept. 26, 1944. On October 10, after the last injection, a small infiltration occurred. She was then given purified insulin and no infiltration occurred. On attempts to resume administration of ordinary insulin, infiltrations once more appeared. A fresh attempt on Dec. 14, 1046, gave the same result. The last control injections were made on Dec. 13, 1947; satisfactory results were obtained with the recrystallized insulin.

CASES OF PATIENTS IN URGENT NEED OF RECRYSTALLIZED INSULIN

CASE 8.—The patient, a man aged 20 years with recent diabetes, was started on insulin therapy in January 1948. Swelling and cutaneous irritation followed the injections. Another type of insulin was tried, but without satisfactory results. Injection in the thighs gave rise to considerable inflammation and swelling above the knee. Injection in the arm and in the chest resulted in similar symptoms.

On February 19 another preparation of insulin, with a purity of which the patient was unaware, was given. It had been recrystallized seven times. Sixteen units, as before, was injected at 8 a.m. During the first few days a small red mark was apparent at the site of injection, but disappeared during the night. By February 24 the injections could be given without subsequent reactions. The general condition of the patient improved daily. After March 1 the syringe was boiled only once a week instead of every day as previously. The aforementioned type of insulin was given until March 6, i. e., for seventeen days.

Then an insulin recrystallized once was given for five days. No visible local reactions occurred, but from the second day the patient felt uneasy. On the third day diarrhea occurred, and it lasted for several days. On March 3 an insulin recrystallized five times was given, and its use was continued until March 29. Diarrhea ceased on the second day. There were no local reactions with the exception of tenderness in the axilla on some days. There was little uneasiness on the first days, but during the last ten days the patient's strength increased.

The symptoms appearing after the injection of commercial insulin with 18 units per milligram of dry substance were in sharp contrast to those previously described. Even when the syringe was boiled every day, a swelling occurred on the thigh on the first day. This regressed during the night, but a similar one appeared after injection on the following day. There was a large swelling on the thigh on the third day. Diarrhea occurred on the third day, but it might possibly have been connected with an epidemic of "gastric influenza" at the patient's place of work. On April 6 the area of swelling on the thigh had decreased to 10 by 6 cm. in diameter and 1.5 cm. in width. It decreased still more subsequently, but at the site of injection the thigh was indurated and tender. Otherwise the patient felt well.

It is evident that the local reactions following the use of ordinary insulin were due to impurities in it, since two preparations of the purified insulin were tolerated. It is possible that the diarrhea occurring on the two occasions when administration of the purified insulin was stopped was caused by an allergic intestinal spasm due to impurities in the insulin. In any case the treatment of this patient would have been difficult or even impossible without recrystallized insulin.

CASE 9.—A man aged 20 years had diabetes since December 1947. Insulin therapy was started in February 1948. Two doses of 20 units each were first given and then two doses of 32 units each every twenty-four hours. During the subsequent days, redness and swelling appeared at the site of injection and the adjacent lymph glands were swollen. At the end of February the patient was given on trial four different preparations in numbered bottles, each containing 400 units.

The first test (bovine insulin recrystallized seven times) caused no tenderness and only slight redness at the site of injection. The second (bovine insulin recrystallized once) in the same dose caused neither redness nor tenderness. The third test (recrystallized five times) caused only insignificant cutaneous redness. The fourth test (less pure insulin with 17 units per milligram) gave rise to considerable redness and tenderness and swelling of the adjacent lymph glands.

In April 1948 a test was made again with the same insulin with 17 units per milligram (two doses of 16 units each every twenty-four hours). This resulted in "red patches and tenderness at the site of injection." The patient subsequently used four ampules of a recrystallized insulin, without discomfort.

COMMENT

According to Wilder,[21] perhaps 1 in every 10 patients who begin treatment with insulin has mild swelling, redness and itching of the skin at the sites of injection. Because of the high frequency of these reactions it is of importance to know what measures should be taken against them. It must first be borne in mind that most of the patients showing mild localized reactions to insulin at the sites of injection lose their sensitivity after continuing the use of insulin for several weeks. Therefore no unnecessary steps should be taken immediately. The majority of the 300 patients who temporarily received the recrystallized insulin in Sweden during 1942 to 1947 were able, after some time, to resume the use of commercial insulin.

Serious general reactions are fortunately rare. Yasuna [1] did not find any instance of such among 3,323 diabetic patients treated with insulin at the Boston City Hospital. Allan and Scherer [12] stated that only 1 to 2 per cent of all the patients sensitive to insulin exhibit general manifestations. Patients allergic to insulin in whom resistance to insulin develops simultaneously are rare.

When serious local reactions such as swelling, induration and pain persist or general reactions such as urticaria, angioneurotic edema, nausea or diarrhea appear and make treatment with insulin difficult, the preparation being used must be replaced. An insulin of a higher

21. Wilder, R. M., in discussion on Gastineau and Leavitt.[24]

degree of purity is then indicated, at least in the event that a trial with other brands of insulin fails. It is possible that not only such suggestions as the use of histamine (Collens, Lerner and Fialka,[22] 1934), histamine and histaminase (Roth and Rynearson,[23] 1939) or of benadryl* and similar compounds (Gastineau and Leavitt,[24] 1946) but also the desensitization procedures will prove superfluous if recrystallized insulin is available, or protamine zinc insulin prepared from recrystallized insulin.

In none of the approximately 300 patients who, among a total of 15,000 diabetic patients in Sweden treated continuously with insulin, have since 1942 received insulin recrystallized once or more has any discomfort remained after changing to one of these types of insulin. Only about 20 of these patients have required such preparations of insulin for a long period.

As regards the question of the insulin itself as an allergen, some light has been thrown on the problem by the experiences reported here. These cases speak in favor of the assumption that both local and general side effects of insulin are caused by impurities accompanying the insulin. True insulin allergy must be considered as extremely rare.

SUMMARY

Mixed beef and pork insulin recrystallized several times has been used in Sweden during the last five years by about 300 diabetic patients showing localized or general reactions to insulin. All of them were able to use the recrystallized insulin without any complications. Most of the patients could soon resume the use of commercial insulin. Only a small number, about 20, needed a three to five times recrystallized insulin constantly. The purest insulins tried were recrystallized seven times.

In a number of patients with severe allergic reactions to commercial insulin it could be stated that the allergic hypersensitiveness to insulin disappeared in the course of time.

The allergic reactions to insulin are considered to be caused by impurities in the insulin preparations irrespective of whether they are crystalline or not.

22. Collens, W. S.; Lerner, G., and Fialka, S. M.: Insulin Allergy: Treatment with Histamine, Am. J. M. Sc. **188**:528, 1934.

23. Roth, G. M., and Rynearson, E. H.: The Use of Histamine and Histaminase in the Treatment of Allergic Reactions to Insulin, Proc. Staff Meet., Mayo Clin. **14**:353, 1939.

24. Gastineau, C. F., and Leavitt, M. D.: Treatment of Allergy to Insulin with Benadryl: Report of One Case, Proc. Staff Meet., Mayo Clin. **21**:316, 1946.

ASCORBIC ACID DEFICIENCY IN THE AFRICAN DISEASE ONYALAI

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ONYALAI was first described by Wellman,[1] in 1904. He and, shortly afterward, Massey [2] reported cases observed in Angola. Since then, various investigators have reported cases in many parts of Africa. A number of theories as to the cause of the disease have been advanced, but as recently as November 1946 Retief [3] stated that its etiology was unknown. There is general agreement that onyalai is a form of thrombopenic purpura, with prolonged bleeding time and normal blood coagulation time. The disease is characterized by the formation of distinctive hemorrhagic bullae on the mucous membranes, most frequently in the mouth. Nasal hemorrhages are often seen. Postmortem examination shows extensive areas of hemorrhage, and death appears to result from severe loss of blood.

During the past twenty years 150 patients with onyalai have been admitted to our hospital; until 1940 no effective treatment was available. Like other workers, we found that the mortality was high. In our hospitalized patients it reached 90 per cent, in spite of various treatments used prior to the trial of ascorbic acid (only patients with severe cases of onyalai seek hospital aid in Angola). Observations on food habits indicated that patients had subsisted on a low intake of ascorbic acid. This factor prompted a trial of therapy with ascorbic acid, a procedure found to be highly effective when large doses were given. At first synthetic ascorbic acid was not available, and lemon juice was used. From detailed observations on 57 patients, as reported, we have been led to conclude that the predisposing cause of onyalai is a deficiency of ascorbic acid.

GENERAL OBSERVATIONS

From the 150 patients seen during the twenty years previous to this report, a great deal of information has been gathered regarding the vari-

1. Wellman, F. C.: Brief Conspectus of the Tropical Diseases Common in the Highlands of West Central Africa, J. Trop. Med. & Hyg. **7**:52, 1904.

2. Massey, A. Y.: Onyalai—A Disease of Central Africa, J. Trop. Med. & Hyg. **7**:269, 1904.

3. Retief, F.: Onyalai, Proc. Transvaal Mine M. Officers' A. **26**:288, 1946.

ous aspects of the disease. As seen in Angola, the characteristic symptom is the appearance of hemorrhagic bullae, varying in size from that of a pea to ½ inch (1.3 cm.) in diameter. The accompanying photograph shows a bulla on a native's tongue. The bullae occur on the tongue, gums, palate or pharynx. Sometimes the vesicles are so extensive that the whole mouth appears to be a hemorrhagic, fungating mass; severe nasal hemorrhages are commonly associated with this condition. Frequently great loss of blood occurs from the urinary tract, the gastrointestinal tract and the uterus. Subconjunctival hemorrhages are common, and in a few cases petechiae have been observed on the

Bulla of onyalai on the tongue of a native.

skin of the arms, legs or body. Severe hemorrhages are often followed by death in one to three days. The vesicles appear suddenly in some patients who have been in apparently good condition before the onset of actual symptoms. Others, however, complain of malaise, aching bones and headache prior to the appearance of the bullae. Besides the acute form of the disease, we have frequently seen a chronic type, which may last from a few months to several years. The majority of patients with this type exhibit unhealthy gingival margins; at intervals bullae appear on the mucous membranes. In some patients small vesicles are constantly appearing, while in others the bullae are of yearly occurrence and are most common during the hunger months.

Onyalai occurs mainly in Africans. Stein and Millar,[4] in 1943, reported the disease in 2 men, a young European and a Chinese. Of the 150 patients in our series, all but 5 were Africans. The exceptions were 1 Portuguese man, 1 Englishman, 2 Portuguese children and 1 adolescent mulatto. Sex distribution among the natives was about equal, and the disease was seen in patients of all ages, from infancy to 65 years. In the past four years we have seen bullae in the mouths of 4 nursing babies. The claim has been made that onyalai occurs mainly in young men; our records show that such has not been the case in this series.

DIET

The diet of the African native in Angola is deficient in almost every nutrient except carbohydrate. During November, December and January hunger is prevalent. Devitalized corn meal forms the bulk of the diet. Dried beans are eaten several times a week. Green leaves, such as those of manioc or squash, are cooked in an open pot with water and eaten several times a week. Other foods are cooked manioc roots, sweet potatoes (when available, near Christmas) and fresh corn (at about the same time). Fruits and vegetables form only a small part of the food supply. Milk and eggs are not used; meat and fish are eaten, on the average, once a week. From an inspection of the food supply there appear to be insufficiencies of essential amino acids, fat and all vitamins and minerals, particularly ascorbic acid, riboflavin and calcium.

Questioning of patients provided the information that fruit and other sources of ascorbic acid had been missing from the food intake prior to the onset of the disease. This was particularly evident in an orphanage, in which one fifth of the children had the disease. The children with onyalai were cured with large amounts of lemon and orange juice, and no further cases appeared in the orphanage after fruit was included in the daily dietary.

Of 57 cases of hospitalized patients studied in detail, onset of symptoms began in 33 in December, January or February; 21 cases were recorded in December, at the height of the hunger season. This seasonal incidence gives further support to the deficiency explanation of the disease. Recurrences frequently occur during the hunger season in patients with the chronic type of onyalai, and in those who have recovered from acute attacks but have returned to the ordinary village diet. From observations made on 22 of the 57 patients studied, we have concluded that an adequate intake of ascorbic acid in the diet prevents relapses. After cure, only 2 of the 22 patients had slight recurrences,

4. Stein, H. B., and Millar, E.: Acute Thrombocytopenic Purpura Associated with Hemorrhagic Bullae with Special Reference to Onyalai, South African J. M. Sc. **8**:1, 1943.

and these patients had not followed the prescribed diet, which contained foods with adequate ascorbic acid content. Fifteen of the 22 were symptom free for periods varying from five to seven years and 5 for one to five years.

TREATMENT WITH ASCORBIC ACID

Since a deficiency of ascorbic acid appeared to be a predisposing factor, it seemed reasonable to use this vitamin in treatment. Until recently synthetic ascorbic acid was not available in our hospital, and lemon juice was used. Lemon juice was administered to 43 of the 57 patients; all but 1 recovered within a few days. The total amounts given were large, ranging from 2 to 20 liters. Such large amounts appeared necessary, but no information on minimal effective doses is available at the time of writing. Some patients were unable to retain lemon juice given by mouth; many with the acute disease were unable to swallow because of the condition of the mouth and throat, while some patients were in a moribund state when admitted. Since ascorbic acid per se was unavailable, lemon juice was given intravenously. For this purpose, a solution was prepared by withdrawing the juice aseptically from the fruit which had been immersed for one minute in boiling water, filtering the juice through sterile gauze and mixing the filtrate with sterile saline solution. With the exception of chills in a few patients, no complications arising from the intravenous injections were observed, and veins were unharmed.

REPORT OF A CASE

The patient was moribund on admission, with cold hands and feet, and the pulse was barely perceptible. Bullae were present on the tongue and in the mouth. There was profuse hemorrhage from the mouth, nose, intestine and bladder. The patient was given 100 cc. of lemon juice intravenously in 1 liter of saline solution. Within two hours the hemorrhages had nearly stopped and the patient regained consciousness. Oral administration of lemon juice was begun and continued for fourteen days. Cure then seemed complete, and the patient was discharged from the hospital.

In many patients, however, response was obtained with intravenous injections of 10 to 15 cc. of lemon juice diluted with equal amounts of saline solution, given two or three times daily. Oral administration of lemon juice to these patients was begun as soon as possible.

When synthetic ascorbic acid became available to us, it was used in the treatment of 10 patients; 9 recovered, and 1 died during treatment. The total amounts of ascorbic acid used varied from 2 to 8 Gm. All 9 patients recovered within seven days.

While prompt relief was obtained within a few days in most cases, a few patients showed bullae and spongy gums, with small hemorrhages, for several months, despite maintenance on diets containing citrus fruits.

Eventual recovery was obtained in all these cases with the continued use of diets adequate in all nutrients, and with an especially good content of citrus fruits, for periods varying from one to six months. One girl who had had persistent symptoms for eight years showed no further sponginess of the gums or bullae after six months of dietary treatment. She has been symptom free for four years at the time of this report.

COMMENT

An examination of the food intake of patients with onyalai gives the impression that a deficiency of ascorbic acid is a predisposing factor, and treatment with ascorbic acid gave prompt recovery; from these two observations it might be concluded that onyalai is a manifestation of ascorbic acid deficiency, dietary in origin. However, it may be that another factor is involved. It was possible to determine approximately the amount of ascorbic acid in the urine of 3 patients: All showed excretions of 50 to 100 mg. of ascorbic acid per twenty-four hours at times of severe hemorrhage, while normal Africans had excretions below this range. It may be postulated that, despite small intakes of ascorbic acid, large amounts are excreted and any body stores rapidly depleted by some toxic mechanism. Further confirmation is given this hypothesis by the dose of ascorbic acid apparently necessary for recovery, a dose much in excess of that required for the treatment of scurvy. At present we are unable to supply further evidence on this point, but it is hoped that continued investigation will determine whether a toxic factor is operating in addition to the dietary lack of ascorbic acid.

SUMMARY

Onyalai, an African disease characterized particularly by hemorrhagic bullae, accompanied with profound thrombopenic purpura, occurs in persons with a dietary history of low intake of ascorbic acid. Without treatment death occurs in about 90 per cent of patients hospitalized in Angola. Treatment with massive doses of ascorbic acid is highly effective. There is a suggestion of a toxic factor, in addition to the dietary deficiency.

Missão de Chissamba.

RETINAL ARTERIOVENOUS NICKING

A Long Term Study of the Development of Arteriovenous Nicking in Hypertensive Patients

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THE FIRST paper of this series was a report in 1942 of the relation of retinal arteriovenous nicking to the size of the heart in ambulatory hypertensive patients.[1] The studies which were reported on at that time began in the late 1930's, and within the past two years my colleagues and I have had the opportunity to reexamine some of these earlier patients. During the earlier studies we made careful notes on the appearance of each lesion, in particular those of retinal arteries, so that we were able in this reexamination a decade later to note the changes in the lesion that had taken place over the years. The present report deals with the results of such examinations.

In our first paper we saw a need for careful evaluation of the various degrees of arteriovenous nicking. Prior to this time, we could find no report that the lesion varied in degree. References to the defect simply describe it as arteriovenous nicking.[2] However, it had been apparent to us for a long time that there was a striking difference in appearance and in the significance of the early and late lesions. At that time we decided categorically to recognize three degrees of arteriovenous nicking and refer to these stages as early, moderate and definite arteriovenous nicking (fig. 1). When we set up this categoric classification in 1938, we had no sure way of knowing that the so-called early lesion developed into the moderate and the moderate into the fully developed lesion. We inferred that such was true because of the increasing destructive appearance of the lesion and also because of the statistical relationship of the various stages to the size of the heart as

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1. Shelburne, S.; Hawley, J. L., and McGee, A. S.: Retinal Arteriovenous Nicking: Relation to Enlargement of the Heart in Ambulatory Patients with Hypertension, Arch. Int. Med. **69**:213 (Feb.) 1942.

2. Gunn, R. M.: Peculiar Appearance of the Retina in the Vicinity of the Optic Disk Occurring in Several Members of the Same Family, Tr. Ophth. Soc. U. Kingdom **3**:110, 1883. O'Hare, J. P., and Walker, W. G.: Arteriosclerosis and Hypertension, Arch. Int. Med. **33**:343 (March) 1924. Friedenwald, J. S.: The Pathology of the Eye, New York, The Macmillan Company, 1929.

Development of the Arteriovenous Nicking in 15 Patients

Case	Age, Yr.	Onset of Hypertension	Cardiac Symptoms	Renal Symptoms	Cerebral Symptoms	Blood Pressure	Arteriovenous Nicking	Size of Heart	Electrocardiogram	Urine	Reaction to Wassermann Test	Comment
1	70	1933	1938 Dyspnea (++) 1947 None	1938 None 1947 None	1938 Vertigo 1947 Vertigo	150/ 95 - 220/120 Average, 190/110	1938 Early 1947 Moderate	1938 Not enlarged 1947 Not enlarged	1938 Normal 1947 Left axis deviation	1938 Normal 1947 Normal	Negative	Hypertension 15 yr.; moderate arteriovenous nicking; no enlargement of heart
2	71	1938 Smothering spells 2 yr.	1938 Dyspnea (+), no edema, pain (+) 1945 Auricular fibrillation, edema (+), S.O.B. (+++)	1938 Nocturia (++) 1947 Nocturia (++)	Dizziness (+)	150/ 90 - 200/130 Average, 180/110	1938 Early 1947 Moderate	1938 Not enlarged 1948 Enlarged	1938 Normal, left axis deviation 1945 Spell of fibrillation 1947 Normal, left axis deviation	1938 Normal 1947 Normal	Negative	
3	77	1936?	1938 Angina 1946 Angina and dyspnea (++)	1938 None 1946 None	1938 None 1946 None	150/100 - 240/150 Average, 200/115	1938 Early 1946 Definite	1938 Not enlarged 1946 Enlarged	1938 Normal 1946 Cove-shaped S-T segment	1938 Normal 1946 Normal	Negative	
4	46	1938?	1939 Dyspnea (++) 1947 Dyspnea (++)	1939 Nocturia (++) and urethritis 1947 Nocturia (+); normal pyelogram	1939 None 1946 Light stroke	160/100 - 220/120 Average, 190/100	1939 Early 1947 Moderate	1939 Not enlarged 1947 Not enlarged	1939 Left axis deviation 1947 Left axis deviation	1939 Normal 1947 Normal	Negative	
5	61	1938?	1938 Dyspnea (+++) 1937 Dyspnea (+++)	1939 Nocturia 1947 Nocturia	1939 Vertigo 1947 Vertigo	140/ 90 - 240/140 Average, 190/110	1939 None 1946 Early, 1 nick 1947 2 early nicks	1939 Not enlarged 1946 Enlarged	1939 Left axis deviation, inverted T_1 and T_2 1944 Same	1938 Normal 1947 Normal	Negative	
6	53	1938?	1939 None 1947 Dyspnea (+++)	1939 None 1947 None	1939 Vertigo (++++) 1947 Vertigo (++++)	200 - 270 Average, 220/140	1939 Early, caliber changes 1947 Early, caliber changes	1939 Enlarged (+) 1947 Enlarged (+++)	1939 Left axis deviation, diphasic T_1 and T_2 1947 Left axis deviation T_1 inverted	1939 Normal 1947 Albumin (+++)	Negative	
7	63	1932	1939 None 1947 None	1939 None 1947 None	1939 Vertigo (+) 1947 Vertigo (+)	140/ 90 - 170/115 Average, 160/105	1939 None 1940 None	1939 Not enlarged 1947 Not enlarged	1939 Normal 1947 Normal	1939 Normal 1947 Sugar	Negative	

8	48	1940?	1940 None 1947 None	Bilateral hydronephrosis (+)	Dizzy spells	155/100 - 230/128 Average, 210/115	1940 Early 1947 Early	1940 Not enlarged 1947 Not enlarged	Normal; no axis deviation	1940 Normal 1947 Normal	Negative Kline positive (++++)	
9	57	1939?	1939 None 1947 None	Nocturia only	None	150/ 90 - 210/120 Average, 190/110	1949 Definite in 2 places in inferior temporal artery OS 1947 Silver wire beyond second nick	1940 Enlarged 1948 No change; apex 1 to 2 cm. outside midclavicle line	1940 Left axis deviation 1947 Left axis, inverted T_1 ectopic beats	1939 Albumin (+) 1949 Albumin (++++)	Negative	
10	63	1927	1939 None 1947 None	1939 Nocturia (+++) 1947 Nocturia (+++)	1939 None 1947 None	150/ 90 - 210/120 Average, 190/110	1939 Moderate 1947 Moderate	1939 Not enlarged 1947 Not enlarged	1939 Left axis deviation 1947 Left axis deviation	1939 Normal 1947 Normal	Negative	
11	45	1940?	1941 Orthopnea 1947 Orthopnea	1941 None 1947 None	1941 Dizzy (+) 1947 Dizzy (+)	130/ 80 - 180/120 Average, 160/105	1942 None 1947 None	1941 Not enlarged 1947 Not enlarged	1942 Inverted T_1 and T_2 1947 Normal	1942 Albumin (++) 1947 Normal	Negative	Electrocardiogram improved despite hypertension
12	43	1939?	1939 Dyspnea (++) and edema (++)	1939 Nocturia (++) 1947 Nocturia (++)	1939 Vertigo (+) 1947 Schizophrenia	160/ 90 - 200/130 Average, 180/105	1939 None 1947 None (sheathing)	1939 Not enlarged 1947 Not enlarged	1939 Normal 1947 Normal; no axis deviation	1939 Normal 1947 Normal	Negative	Periarterial sheathing developed but no arteriovenous nicking
13	59	1938?	1940 Dyspnea (++++) 1946 Dyspnea (++) Angina (++)	1940 Nocturia (6 to 10 times) 1947 Same	1940 Vertigo (++++) 1947 Vertigo (++)	190/ 94 - 290/150 Average, 230/120 1940 and 1945 Average, 200/115 1945 and 1946	1940 None 1947 Moderate small hemorrhage, caliber (+++)	1940 Enlarged 1947 Enlarged	1940 Low T_1 and T_2 1947 Deep inversion of T_1 and T_2	1940 Normal 1947 Normal	Negative	
14	70	1941?	1941 None 1946 None	1941 None 1946 None	1941 None 1946 Vertigo (+)	160/100 - 220/140 Average, 190/115	1941 None 1946 Early	1941 Not enlarged 1946 Enlarged	1941 Left axis deviation, flat T wave 1946 Same	1941 Normal 1946 Normal	Negative	
15	82	1930 (220)	1941 Dyspnea (++) 1947 Dyspnea (+++), edema (++) and cardiac infarct (old)	Kidneys small	1941 Vertigo 1947 Vertigo	160/ 80 - 200/110 Average, 170/100	1941 Moderate 1946 Same (no change)	1941 Enlarged 1947 Enlarged	1947 Left axis deviation, diphasic inversion of T wave	1941 Albumin (trace) 1947 Albumin (100 mg.)	Negative	Died from gastric hemorrhage (ulcer) June 17, 1947; moderate arteriosclerosis

The approximate date of the onset of hypertension is listed, but the figures are far from accurate and should be regarded in most cases as guesses.

determined by careful roentgenologic studies.[1] Enlargement of the heart was present in less than half the patients who showed early arteriovenous nicking, but it was present in 85 per cent of the patients with the moderate lesion and in 95 per cent with fully developed arteriovenous nicking. Until this present study, however, we had never actually demonstrated the development of one lesion into the other, and we have been unable to find any reference in the literature to any observation of this sort. We are now able to state positively that the inference is correct, and indeed, the gradations of arteriovenous nicking represent a development that takes place over a period of many years in hypertensive patients. This is well shown in the table.

The reexamination of these patients has shown that it requires many years of well developed and persistent hypertension with especially increased diastolic pressures to produce the definite lesion. It

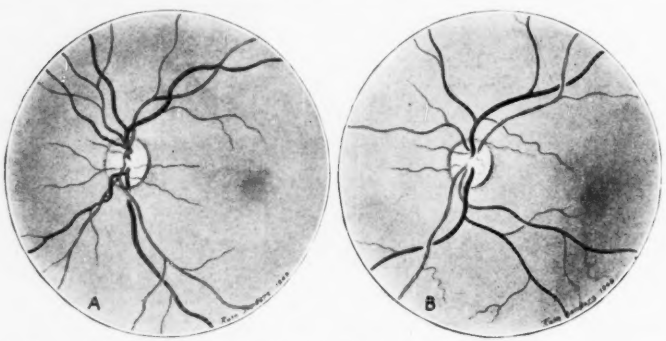

Fig. 1.—*A*, two examples of early arteriovenous nicking in the superior temporal artery and moderate arteriovenous nicking in the inferior temporal artery. Note that in the moderate lesion there is no true gap between the artery and the two ends of the vein. This distinguishes the moderate lesion from the definite. *B*, definite arteriovenous nicking in the superior temporal and inferior temporal arteries. The lesion in the superior temporal artery shows clearly a gap between the ends of the vein and the artery and the clubbing at the ends of the vein. The crossing in the inferior nasal artery shows the gap between the ends of the vein and the artery, but in this lesion the end of the vein is pointed. Note the marked localized caliber changes in the arteries. This patient had long-standing moderate hypertension, which finally developed into the high diastolic type or rapidly progressing hypertensive vascular disease.

never occurs in the nonhypertensive person. We have seen patients who have had high systolic pressures and diastolic pressures in the 90 to 95 range who had no arteriovenous nicking after twenty-five years.

It is doubtless worth while to call attention to a few of the patients whose symptoms are listed in the table. The patient in case 3 had moderate hypertension; in the retina we found an early lesion in

1938, which by 1946 had become a definite lesion, and during that period the heart became enlarged. In cases 1 and 2 the early lesion developed into a moderate lesion from 1938 to 1947; in case 1 the heart did not enlarge in that period, but it did enlarge in case 2. The patient in case 6 had severe hypertension and was rather remarkable in that early arteriovenous nicking present in 1938 was still present in 1947. In this patient, however, there were extensive local and general caliber changes in the arteries on both examinations. A study of the table shows the remarkable variation in the development of arteriovenous nicking in different patients, which is a common experience in the study of any type of arteriosclerosis. Some persons seem to be far more susceptible to the development of the lesion than others, even when the blood pressure is at moderate to high levels. The table also shows the progressive lesions in the heart as shown by increase in the size and changes in the electrocardiogram. Unfortunately, because of shifts in population, we were not able to reexamine a sufficient number of our earlier group to make any statistical study which would be valuable in prognosis, but an ample number of cases are recorded in the tables to establish clearly the development of arteriovenous nicking.

COMMENT

It is of importance that the various degrees of arteriovenous nicking be recognized in the course of the physical examination and so recorded, because the significance of the early lesion is so different from the significance of the more severe lesions. Although one cannot make a prognosis on the basis of these lesions, it is obvious that they give a strong clue to the stage of the development of the hypertensive state in any given patient under scrutiny. This was shown in our early work, in which there was a definite relation between the severity of the arteriovenous lesion and the size of the heart, and it is confirmed by the present long term reinvestigation.

SUMMARY

Drawings made from actual patients showing the various degrees of retinal arteriovenous nicking, early, moderate and definite, are presented.

Study of 15 cases over a long period has proved that early arteriovenous nicking progresses to moderate or definite arteriovenous nicking over a period of years and that the categoric classification previously reported actually represents degrees of the same lesion. These cases show in some measure the time required for progression from one degree of the lesion to the other and the many years required for the formation in hypertensive patients of the fully developed lesion which we have called definite arteriovenous nicking.

CLINICAL DIFFERENTIATION OF VARIOUS TYPES OF NONTOXIC NODULAR GOITER

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THE PURPOSE of this paper is to indicate which facts in the history and examination of a patient aid in the differential diagnosis of nontoxic nodular goiter. The nodules may be involutionary, neoplastic or, more rarely, sites of thyroiditis. From July 1935 to July 1941, 242 patients with nontoxic nodular goiter were seen in the University of California's thyroid clinic. Sufficient data, follow-up observations and pathologic specimens were available to permit consideration of 114 cases in this study. Gross specimens and histologic sections of the glands were studied, and, with these data as a base line, an attempt was made to correlate the clinical features with the pathologic diagnosis of this condition.

PATHOLOGIC CLASSIFICATION

Involutionary Nodules (72 cases).—The investigations of Marine[1] seem to have established that involutionary nodules in the thyroid gland are formed by cyclic hyperplasia and involution. This waxing and waning of local acinar activity and of colloid storage is probably correlated with the iodine needs of the gland, which vary and which seem to be increased by the added strain of infections, the menarche, pregnancy and the menopause. Further growth of the nodules may be affected by cyst formation; by hemorrhagic, calcific or hyaline degeneration, or by proliferation of the acinar elements. The adjacent compressed thyroid tissue forms a pseudocapsule of fibrous tissue, which more or less demarcates the nodules from the remainder of the gland. Thus, it is clear that these nodules are in no

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1. Marine, D.: The Pathogenesis and Prevention of Simple or Endemic Goiter, J. A. M. A. **104**:2334-2341 (June 29) 1935.

sense neoplasms. Histologically, the acini within the nodules may be seen to be of varying size, and abundant colloid is present. Areas of epithelial budding and proliferation are not infrequent, especially near the central portion of the nodules. Involutionary nodules are usually multiple.

Adenomas (18 cases).—These nodules, in contradistinction to involutionary nodules, are neoplasms. They are circumscribed and encapsulated. The cut surface is homogeneous, relatively devoid of colloid and glistens, with a pinkish tan color. Edema or hemorrhagic degeneration may occur, especially centrally. Warren[2] stated that, in addition to the features noted, the histologic appearance of the adenoma is usually distinctly different from that of the surrounding gland. Variation in acinar structure within the adenoma may occur in combinations of embryonal, fetal, simple or colloid patterns. The cells and nuclei are uinform, and mitotic activity is not abnormal.

Carcinomas (21 cases).—These tumors may vary from nodules of less than 0.5 cm. in diameter to large, bulky masses, extending beyond the confines of the gland. The cut surface varies with the differentiation, the more differentiated tumors displaying meager colloid, while the more anaplastic ones are less homogeneous, are usually devoid of colloid and show wider extraglandular spread. Hemorrhagic and other forms of degeneration are common, especially in the more cellular tumors. Microscopically, the carcinomatous tissue may present a glandular or papillary pattern or densely packed sheets of anaplastic cells. Mitotic activity is pronounced, and capsular and vascular invasion are frequent. It is important that a diagnosis of carcinoma in this series was never made on the basis of mere cellular changes alone; invasion, of one type or another, was invariably present.

Unclassified Nodules (3 cases).—The nodules in these cases could not be classified as to neoplastic or involutionary origin. These cases were not included in the statistical calculations, but the nodules are described here for completeness of classification. The major difficulty in distinguishing a neoplastic from an involutionary nodule is that an adenoma may differentiate and form colloid, thereby mimicking an involutionary nodule, while, on the other hand, an involutionary nodule may contain such large areas of acinar proliferation that a neoplasm is simulated. It is our opinion that this proliferative reaction in involutionary nodules in certain instances indicates the site of development of a carcinoma. In any event, the proliferating epithelial tissue obscures most evidence of the involutionary genesis of the nodule, and no precise classification is possible.

2. Warren, S.: Tumors of the Thyroid, Bull. New York Acad. Med. **23**:5-9, 1947.

DIFFERENTIAL DIAGNOSIS

The table indicates 96 female patients and 15 male patients with these disorders, a ratio of 6.4:1. Although the number of cases in the present series is small, this is essentially the proportion noted by Means (7:1).[3] He suggested that the reason for the frequent occurrence of goiter in women is a lower power of utilization of iodine, coupled with the probable antagonistic effect of ovarian secretion on the thyroid. The latter factor may explain the more frequent appearance of goiter at puberty in girls than in boys and the transient enlargement of goiters at the time of pregnancy. However, it would not account

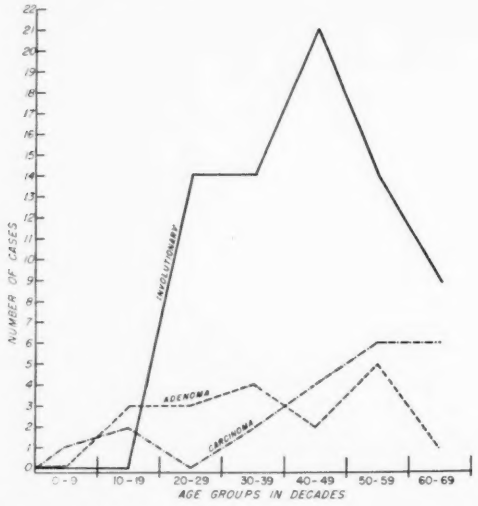

Fig. 1.—Age distribution of patients with adenomas, carcinomas and involuntary nodules of the thyroid.

for the appearance of goiter at the menopause. The age of a patient with nontoxic nodular goiter is of decided importance in one respect: a nodular goiter is far more likely to harbor a neoplasm in a person under 20 years of age than in an older person (fig. 1).

It is frequently difficult to decide whether a patient is from a region in which goiter is endemic. However, according to data in the acompanying table, 77 per cent of patients with involutionary nodules were from endemic areas. Only 33 per cent of patients with carcinoma

3. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937.

were from endemic areas, but in so small a number of cases these differences are not statistically significant.

Some question has arisen as to just what constitutes a positive family history of goiter. Means [3] stated the belief that 10 to 27 goiters per thousand persons occur in the areas where goiter is most prevalent, while only about 1 case per thousand persons is present in nonendemic areas. We feel justified in considering one goiter in a close blood relative of a patient (sibling, parent, aunt or uncle) as significant. One should not lose sight of the fact that the sole known causative factor is environmental lack of iodine, although the effect is enhanced in each succeeding generation in an endemic region. Of the 72 patients with involutionary nodules, 47 per cent had a positive family history of goiter; such a history was given by 55 per cent of patients

Data in 114 Cases of Nontoxic Nodular Goiter

	Patients with Involutionary Nodules	Patients with Adenomas	Patients with Carcinomas
Total	72	18	21
Sex:			
Male	7	2	6
Female	65	16	15
History of residency in endemic area	56	14	7
Family history of goiter	34	10	2
History of growth of lesion	31	12	12
Average duration of goiter	12.7 years	10 years	7.1 years
Prior to symptoms	9.8 years	6.7 years	5.8 years
With symptoms	2.9 years	3.3 years	1.3 years
Single nodule	18	15	10

with adenoma and by less than 10 per cent of patients with carcinoma (table). The latter figures are probably distorted by the small number of patients with neoplastic lesions. These data too are somewhat helpful, but of no crucial clinical significance in an individual case.

Although involutionary nodules may increase in size owing to hemorrhage (often associated with tenderness), cyst formation, proliferation or increased colloid storage, a history of growth of a nodule is helpful in differential diagnosis. Forty-three per cent of patients with involutionary goiter, 66 per cent of patients with adenoma and 57 per cent of patients with carcinoma gave a history of growth of the goiter. A history of recent growth is far more suggestive of neoplasm than a sustained increase in size, characteristic of involutionary goiter.

It seems reasonable that, because of their slower growth, which permits neighboring structures to accommodate to the pressure and displacement, involutionary nodules could be present for a longer time than more rapidly growing, true neoplasms before producing pressure

symptoms. This possibility is not borne out strikingly by the data in the table: Involutionary goiters existed for an average of nearly ten years before causing pressure symptoms, while adenomas and carcinomas produced symptoms 6.7 and 5.8 years, respectively, after inception of the goiter. A neoplasm need not have been present for these prolonged periods, however, as it is probable that neoplasms have often become engrafted on a simple goiter; in addition, the time of origin of the neoplasm is not precisely determinable.

Nearly all symptoms caused by nontoxic goiters are due to pressure on neighboring structures by the enlarged gland. Concomitant symptoms must be differentiated and not attributed to the thyroid gland. In a few patients in the series the symptoms of anxiety states and symptoms associated with the menopause suggested the possibility of thyroid toxicity, but in all instances this factor was ruled out by the results of appropriate tests, including those for basal metabolic rate and galactose tolerance.[4] One patient had a moderate anemia which produced some dyspnea; since this symptom disappeared on medication with iron, it became apparent that the dyspnea had not been caused by tracheal pressure from the goiter.

The frequency of various pressure symptoms is indicated in figure 2. As would be expected, a local sense of fulness was the commonest symptom. Hoarseness, so often considered a sure indication of the presence of a malignant growth, was present in 25 per cent of patients with involutionary goiter, in 27.2 per cent of patients with adenoma and in 38 per cent of those with carcinoma. Dysphagia, dyspnea from mechanical pressure and the subtler complaint of excessive mucus in the throat were about equally common, occurring in a third or less of the patients in each group. Persistent pain in the thyroid, radiating to the ear, the side of the neck or the shoulder, though uncommon, occurred in 3 patients with carcinoma. In general, the type of pressure symptoms does not aid in the differential diagnosis of nontoxic nodular goiter.

Not only were all pressure symptoms fully relieved by subtotal thyroidectomy, but several patients volunteered after operation that their voices were "freer than before" or that they could swallow much more easily. However, sensations at the operative site might persist for several months if a keloid formed.

The consistency of the goiter is not especially helpful in differential diagnosis, because neoplasms may feel relatively soft and meaty to palpation, while involutionary nodules, even if calcification is not present, may be quite firm. Fixation of the goiter to surrounding

4. Althausen, T. L.; Lockhart, J. C., and Soley, M. H.: A New Diagnostic Test (Galactose) for Thyroid Disease, Am. J. M. Sc. **199**:342-351, 1940.

structures and the presence of enlarged cervical nodes are cogent reasons for suspecting the presence of a malignant growth.

One of the most significant diagnostic factors is the presence of a single nodule. Of the involutionary goiters of this series, 25 per cent were solitary nodules, whereas of the adenomas and carcinomas 83.3 and 58.5 per cent, respectively, were single nodules. The importance of

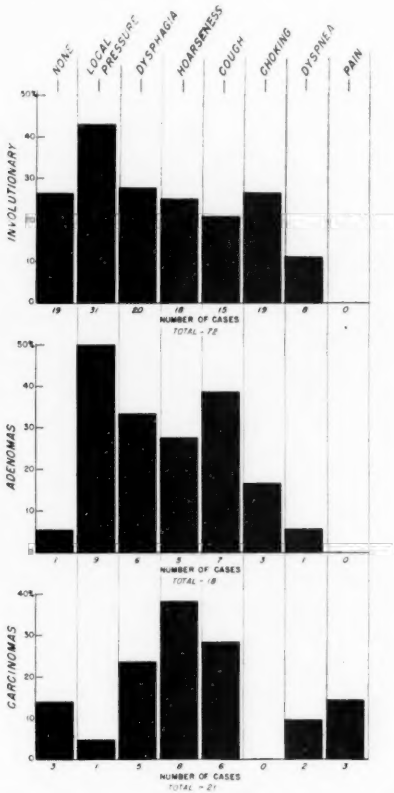

Fig. 2.—Frequency of various pressure symptoms in three types of goiter.

this fact was emphasized in a previous study, in which in a series of 96 solitary nodules of the thyroid, 21.8 per cent were benign and 13.5 per cent malignant tumors.[5] This high frequency of neoplasms among solitary nodules of the thyroid seems to indicate prompt removal.

5. Soley, M. H.; Lindsay, S., and Dailey, M. E.: The Clinical Significance of a Solitary Nodule in the Thyroid Gland, West. J. Surg. **56**:96-104, 1948.

Another important factor is the detection of paralysis of a vocal cord at laryngoscopy, by far the most frequent sign in the group of patients with carcinoma. Of those patients with hoarseness, 11.1 per cent with involutionary nodules and 75 per cent with carcinoma displayed a paralyzed cord. Hoarseness may be caused by tracheal pressure and displacement by any type of goiter, but actual invasion or injury of the recurrent laryngeal nerve is often the causative factor in patients with malignant nodules.

COMMENT

Pressure symptoms due to nontoxic goiter are enumerated in several textbooks, but there is seldom an adequate discussion of their significance. Bram,[6] for instance, listed hoarseness, dyspnea, dysphagia, cough, and even headache and vertigo. Many authors state that hoarseness is an almost pathognomonic sign of a malignant growth, but results in our study fail to bear out this opinion. Plummer[7] reported the effects of pressure of an adenomatous goiter at the thoracic inlet, which caused symptoms suggesting globus. Willius[8] described the case of a man who for many years was considered to have dyspnea due to heart disease. Later the condition proved to be the effect of pronounced tracheal pressure by a goiter; ventilation was adequate at rest, but not during periods of exertion.

The following clinical features should lead one to suspect the presence of a neoplasm: the presence of a nodular goiter in a patient under the age of 20; a history of recent growth (especially if associated with the concurrent appearance of pressure symptoms); the presence of a paralyzed vocal cord, or the identification of a solitary nodule. In regions where surgeons skilled in thyroid surgery are available, such a goiter should be removed.

The technics for thyroidectomy are well known, but we wish to emphasize our belief that no solitary nodule should be merely enucleated. In such instances the homolateral lobe should be fully resected. In cases of manifest malignant thyroid tumors, total thyroidectomy should be carried out, and if any evidence of involvement of the cervical nodes is found at operation, radical dissection of the neck should be carried out. Radiation therapy has been reserved by us for use in cases of inoperable tumors and for relief of specific pressure symptoms in cases of recurrence.

6. Bram, I.: Goiter: Non-Surgical Types and Treatment, New York, The Macmillan Company, 1924.

7. Plummer, W. A.: Compression of the Trachea by an Adenomatous Goiter Situated in the Thoracic Inlet, Proc. Staff Meet., Mayo Clin. **9**:411-413, 1934.

8. Willius, F. A.: Partially Obstructive Dyspnea Simulating Dyspnea of Cardiac Origin, Proc. Staff Meet., Mayo Clin. **11**:46-48, 1936.

Some workers have advocated the removal of all nodular goiters in order to prevent the development of a malignant tumor. In certain instances an involutionary nodule may proliferate and form a neoplasm, but there is no unassailable evidence that such a change occurs more readily in such a site than in a thyroid gland free of clinically recognizable nodules. In the absence of pressure symptoms, there seems no impelling reason to remove a nodular goiter unless some of the clinical points suggestive of neoplasm are present.

SUMMARY AND CONCLUSIONS

In a series of 114 nontoxic nodular goiters, 72 were involutionary, 18 were adenomas and 21 were carcinomas. Three additional goiters could not be classified as to involutionary or neoplastic origin.

The clinical points which suggest the presence of a neoplasm are: occurrence in a patient under the age of 20; a history of recent growth, especially when associated with the concurrent appearance of pressure symptoms; the presence of a paralyzed vocal cord, and the discovery of a solitary nodule. Goiters in such instances should be removed promptly. The type of pressure symptoms, the duration of the goiter's presence and the sex and residence of the patient are not of major importance in differential diagnosis.

The Medical Center (22).

DIABETES AND PREGNANCY

A Clinical Analysis

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THE PROBLEM of pregnancy in the patient with diabetes has intermittently drawn comment from clinicians throughout the period of insulin therapy, but it is only in comparatively recent years that research has brought to light facts which may eventually lead to an understanding of the essential differences between the diabetic and the normal woman in pregnancy. Most physicians have carried too few diabetic women through pregnancies to be familiar with all aspects of the problem, and there are many points on which the literature is still in controversy. Some of these details are subject to clinical analysis of large series of cases, and the literature is not overcrowded with such studies. This discussion reviews the literature and summarizes current opinion on the problem. Our own conclusions are based on information derived from a study of diabetic women at the Charity Hospital of Louisiana, at New Orleans, and throughout the presentation of these observations we compare or contrast them with those of others.

MATERIAL OF THE STUDY

During the ten years between June 30, 1937 and July 1, 1947, the obstetric services at Charity Hospital delivered 55,617 pregnant women. During this time 41 diabetic women were delivered 71 times; 58 of these deliveries occurred during the time the mother was actually diabetic, and 13 occurred during the mother's five prediabetic years. Seven other diabetic women were admitted to the obstetric service but are not included in the statistics for deliveries because they did not come to term under observation. This group of patients includes those reported on by Engelhardt and Melvin.[1]

From 148 other women, who attended the diabetic clinic, obstetric histories were utilized. This group was selected as a result of approximately 250 such interviews;

From the Department of Medicine, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana.

Dr. Patterson is resident in medicine, Charity Hospital, and Dr. Burnstein is graduate assistant in medicine, Louisiana State University School of Medicine.

1. Engelhardt, H. T., and Melvin, J. P., Jr.: The Management of Diabetes Mellitus During Pregnancy, South. M. J. **39**:734 (Sept) 1946.

patients were eliminated from the final group only because their memory for the events seemed inadequate or because they became diabetic after the age of 65, so that their childbearing period was more than twenty years removed from their diabetic years.

All groups contributed to statistics on fertility, miscarriage and fetal and neonatal death. The 71 deliveries in the hospital of the 41 women contributed to the detailed obstetric and medical data such facts as weight at birth, presentation, type of delivery, obstetric and diabetic complications and insulin requirement. No patient was included in whom accepted criteria for the diagnosis of diabetes were not present.

FERTILITY

Priscilla White [2] quoted Bouchardat from 1875 and Naunyn from 1906 as to the rarity of pregnancy in diabetic women in preinsulin years; the former saw no cases, the latter only 1. Later statistics,[3] also from the preinsulin period, gave a fertility incidence of about 2 per cent as compared with the normal 10 per cent. White [2] estimated

TABLE 1.—*Incidence of Conception per Hundred Patients with Diabetes During Their Diabetic and Prediabetic Years*

	Percentage of Total Patients
Diabetic years (both groups)	20.8
Diabetic years (clinic group only)	11.6
Prediabetic years	
0 to 5	12.9
5 to 10	12.3
10 to 15	12.6
15 to 20	12.9

that about 1 pregnancy in 1,000 is in a diabetic woman, and she considers this the expected ratio since approximately 1 woman in 1,000 of childbearing age is diabetic. Our own ratio of 71 in 55,617 approximates this. Since agreement as to the fertility of diabetic women is not complete and further information is needed, we present our statistics in grahic form (fig. 1 and table 1). The ordinate represents pregnancies per hundred patient years. Patients contributed to the total patient years for any given year only if they were diabetic or prediabetic during that year, and of course only pregnancies occurring during corresponding years are included. The inclusion of the five prediabetic years does not alter the curves, since the fertility rate is almost identical in the diabetic and prediabetic years. The curves should therefore be a true index of the diabetic woman's fertility. They would indicate that the diabetic woman is at least as fertile as the normal

2. Joslin, E. P.; Root, H. F.; White, P.; Marble, A., and Bailey, C. C.: The Treatment of Diabetes Mellitus, ed. 8, Philadelphia, Lea & Febiger, 1946.

3. Skipper, E.: Diabetes Mellitus and Pregnancy: Clinical and Analytical Study, with Special Observations upon Thirty-Three Cases, Quart. J. Med. **2**:353 (July) 1933.

woman, perhaps more so. Furthermore, the distribution of her fertile years corresponds to the normal; stated another way, the diabetic woman of whatever age is as fertile as the normal woman of similar age.

Joslin [2] attributed the increasing fertility of diabetic patients to the use of insulin, and we are able to suggest no other explanation for the gross discrepancies between modern and preinsulin statistics for fertility. However, so many of our patients continued to become pregnant in spite of their ignorance of, or indifference to, the use of insulin that we are reluctant to accept this explanation completely. Our opinion is difficult to support statistically. The patients with severe diabetes who require insulin to prevent acidosis of course depend on insulin for their life and health, as well as for their fertility; the patients with mild diabetes, controlled on diet alone, seem equally fertile. It is

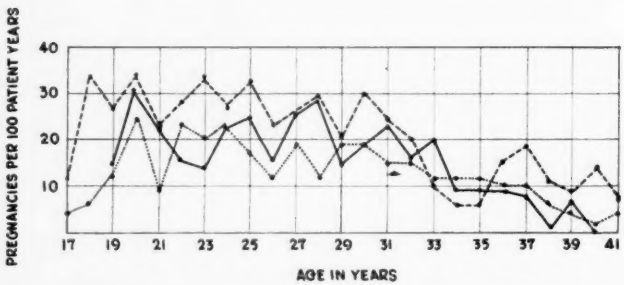

Fig. 1.—Incidence of pregnancies per one hundred patient years in women with diabetes during their diabetic and prediabetic years. The broken line indicates diabetic and prediabetic years for the group from the clinic and delivery room and the unbroken line that for the clinic group only. The dotted line indicates the incidence for the control group.

from the middle group, which may or may not take insulin without drastic change in their immediate state of health, that we have gained the impression that fertility is not closely related to the adequacy of control by insulin therapy.

MATERNAL MORTALITY AND MORBIDITY

The attitude of physicians toward pregnancy in their diabetic patients varies widely, and it is difficult to find in the literature an adequate appraisal of the many problems which may arise. Ewald [4] made the statement that "pregnancy in the severe diabetic is nothing less than a catastrophe." Joslin [2] expressed the opposite extreme of optimism and impressively supported his opinion with a maternal mortality rate

4. Ewald, P. P.: Pregnancy and Diabetes, Journal-Lancet **65**:13 (Jan.) 1945.

of 0.4 per cent in 271 cases. Most available statistics estimate maternal mortality at 3 to 4 per cent, or about six or seven times that for normal women.

Of our 71 deliveries, 4 patients, 2 of them not at term, were in coma; only 1 of them recovered. One of the patients entered the hospital at the eighth month of gestation and a stillborn infant was delivered two days later. She continued febrile and in acidosis and died seventeen days post partum. At autopsy staphylococcic septicemia with multiple abscesses of various sizes was observed. The second patient died of postpartum sepsis twenty days following an abortion in the fourth month. The third patient, to all appearances, died of diabetic acidosis; she was adequately treated only after she had been in coma for twelve hours. This last death, while probably preventable, was nevertheless the one most directly due to the diabetes. The other 2, while primarily due to sepsis, must fairly be included as diabetic mortality because of the diabetic person's predisposition to severe infection.

Twenty of our patients were at various times, near term, in acidosis. In 10 patients, the acidosis was of sufficient degree to occasion morbidity. In 5 of these women, the chief problem in management was the erratic behavior of the carbohydrate tolerance. The tendency of this type of patient to show acetonuria, at times without glycosuria and with low blood sugar level, is alarming and extremely difficult to control. Doses of insulin that in other patients with acidosis would be trifling may produce hypoglycemia. The normal tendency of pregnant women to have lowered carbon dioxide–combining power is exaggerated in diabetic women, and values below 20 volumes per cent may occur, without the usual grave prognostic import of such levels. In these patients vomiting, loss of appetite and other relatively minor upsets may affect the acid-base balance beyond all expectation. It is important to stress the fact that this pattern may be found, inexplicably, in the patient with mild diabetes as well as in the one with the severe form. When the pattern exists in a patient with low blood sugar levels, insulin may have to be used so cautiously that glucose and alkaline infusions will constitute the principle therapy.

The effect of pregnancy on the insulin requirement of the diabetic woman is another problem on which widely divergent opinions have been expressed. The theory that the fetal pancreas contributes to the maternal requirement is apparently without any scientific basis, as there is no evidence that insulin crosses the placenta. On the other hand, in many patients for whom the insulin requirement seems to rise, the increase may be due merely to closer control of the diabetes during the prenatal period. In our patients for whom adequate evidence was available, we observed that the requirement rose in 19, fell in 5 and

remained the same in 38. In the majority of patients the insulin requirement probably will be little affected (fig. 2).

The really important question of how great a threat to life is offered the diabetic woman by pregnancy remains unanswered. Probably, it depends more on the potentialities of uncontrolled or uncontrollable acidosis than on the acidosis or the diabetes per se. In our opinion, with adequate attention, pregnancy should prove no more hazardous a venture than many unavoidable episodes to which the diabetic woman is subject throughout her life, and that only in the rarest of cases will it be necessary to forbid maternity to the diabetic woman.

FETAL AND NEONATAL MORTALITY

It has long been recognized that, whatever the effect of insulin on the mother, its use has not lowered the extremely high fetal mortality of diabetic pregnancies. This fact was effectively demonstrated by Miller, Hurwitz and Kuder [5] when they analyzed the statistics on diabetic

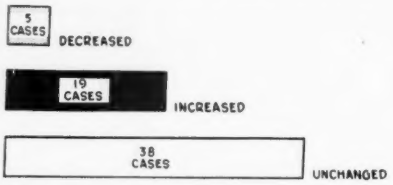

Fig. 2.—Effect of pregnancy on insulin requirement.

pregnancies from the New Haven Hospital, the New York Hospital, and the Boston Lying-in Hospital. They also showed a point not previously recognized, that this high fetal mortality was evident in the pregnancies of diabetic women for as long as twenty years before their diabetic state became manifest. Dolger soon questioned these observations, and, with Herzstein,[6] published statistics from Mount Sinai Hospital, New York, which seemed to show that these abnormalities were to be found no earlier than five years before the development of diabetes. Their data were obtained from interviews with patients in the diabetic clinic, a group that is usually older than patients encountered in a series of deliveries. The authors themselves offered this fact as explanation for the generally lower fetal mortality in their patients. Our percentages are derived from both types of patients, and on finding

5. Miller, H. C.; Hurwitz, D., and Kuder, K.: Fetal and Neonatal Mortality in Pregnancies Complicated by Diabetes Mellitus, J. A. M. A. **124**:271 (Jan. 29) 1944.

6. Herzstein, J., and Dolger, H.: The Fetal Mortality in Women During the Prediabetic Period, Am. J. Obst. & Gynec. **51**:420 (March) 1946.

that the fetal mortality in the clinic group was 23 per cent as compared with 46 per cent in the group of deliveries, we were inclined to agree that older diabetic women were less susceptible to these abnormalities than younger ones. However, when all patients from both groups were considered by age, it was observed that diabetic women over 35 years of age had fetal mortality of 50 per cent, while those under 35 had only 39 per cent mortality. Furthermore, on closer inspection of the pregnancies brought to term by the group seen in the clinic it was noted that most of the live babies were contributed by the few patients in the group who were under 35. We therefore concluded that the older diabetic woman has less chance of obtaining a live baby than does the younger woman (fig. 3).

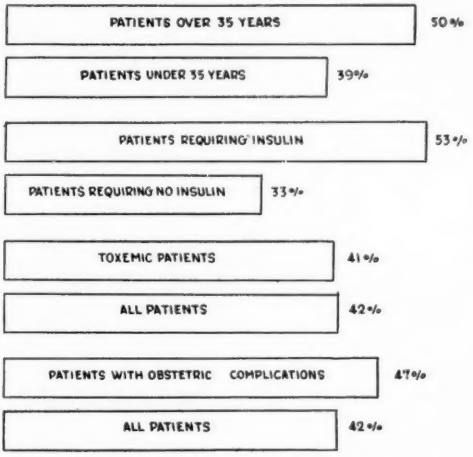

Fig. 3.—Per cent of fetal and neonatal mortality as affected by maternal age, severity of the diabetes, toxemia and obstetric complications.

Our figures, shown in table 2, tend to support the observation of Miller that a high fetal mortality is evident as long as twenty years before the onset of the diabetes. A point on which we differ from accepted views is that the diabetic woman's approximately 20 per cent incidence of miscarriages is not greatly at variance with the estimated incidence for normal women.

FACTORS INFLUENCING FETAL AND NEONATAL MORTALITY

Data on the patients delivered in the hospital were analyzed in more detail and yielded information on several points. Some of this infor-

mation is at variance with previous reports, and some of it may be of value in the appraisal and management of diabetic pregnancies.

The severity of the diabetes, contrary to other opinion,[5] seems to affect the mortality of the fetus to some extent. When the mothers were divided into two groups, those requiring insulin and those who did not require it, the fetal mortality of the insulin-treated group was 53 per cent, as compared with 33 per cent for the untreated group. We do agree, however, that such figures cannot be applied too directly, since a woman with severe diabetes may deliver live babies, while one with very mild diabetes may consistently deliver stillborn infants (fig. 3).

Premature delivery was a frequent occurrence; 12 of 71 deliveries were of babies weighing less than 5 pounds 6 ounces (2,438 Gm.). This prematurity did not seem to affect fetal mortality, since these premature infants survived as often as did those carried to term. It

TABLE 2.—*Incidence of Miscarriages, Live Babies, Fetal and Neonatal Deaths in Diabetic and Prediabetic Years*

	Diabetic Years			Prediabetic Years											
				0 to 5			5 to 10			10 to 15			15 to 20		
Incidence of	Total	No.	Per Cent	Total	No.	Per Cent	Total	No.	Per Cent	Total	No.	Per Cent	Total	No.	Per Cent
Miscarriages	113	24	21.2	81	19	23.5	89	20	22.5	85	12	14.1	86	27	31.39
Fetal and neonatal deaths	113	31	27.4	81	20	24.7	89	15	16.8	85	6	7.06	86	10	11.62
Live births	113	57	50.5	81	42	51.8	89	54	60.7	85	67	78.8	86	49	56.9
Pregnancies reaching term															
Fetal and neonatal mortality	88	31	35.2	62	20	32.3	69	15	21.8	73	6	8.22	59	10	16.9
Live births	88	57	64.8	62	42	66.7	69	54	78.2	73	67	91.7	59	49	83.06

might be supposed that the hazards of prematurity were no greater than those which would have been encountered in the last weeks of gestation.

The average length of labor, fourteen hours, conformed to normal averages and was not seemingly a factor in the death of any infant.

In 69 deliveries, the presentation was vertex in 61 and breech in 8. This 11.5 per cent incidence of breech presentation is in excess of the normal 3 to 4 per cent but is still far less than the 33 per cent quoted by White.[7] The higher figure may perhaps be obtained by including deliveries in the earlier months of pregnancy. In 49 of the cases of vertex presentations delivery was spontaneous; forceps were applied in 7; manual extraction of a shoulder was required in 3, and section was necessary in only 2. The method of delivery in these patients seemed to have little effect on the fetal outcome. In 3 of the breech

7. White, P.: Pregnancy Complicating Diabetes, J. A. M. A. **128**:181 (May 19) 1945.

presentation cases, delivery was spontaneous; in 3 delivery was by extraction, and in 2 section was used. Both of the breech babies delivered by section survived; of those delivered from below, only 2 lived. Of the 4 infants delivered by cesarean section, only 1 was lost, and this mother was evidently not as far advanced in pregnancy as was thought, since the baby weighed only 4 pounds 11 ounces (2,126 Gm.). These groups are obviously too small to have statistical significance, but we are in agreement with the opinion that early section is the surest method of obtaining a live baby. We do not agree, however, that it is the method of choice for all or even for the majority of cases. Too many of the patients were seen to deliver spontaneously a series of live babies, even in the presence of toxemia, to advocate section as a routine procedure. Serial determinations of

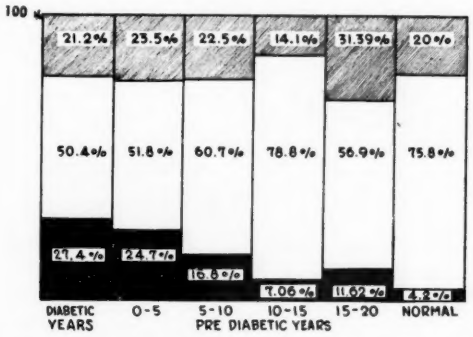

Fig. 4.—Percentages of miscarriages, live babies, fetal and neonatal deaths in diabetic and prediabetic years based on figures in table 2. Gray areas represent miscarriages, white spaces, live births and black areas, fetal and neonatal deaths.

hormone levels may be of great value in designating those cases in which early section, between the thirty-sixth and thirty-eighth week, is needed, but this method has not been available. In its absence the outcome of previous pregnancies will prove a rough, and certainly not infallible, guide as to what may be expected in a current pregnancy. Early section has been advocated principally to avoid fetal death or other changes which usually take place during the last few weeks of gestation and, if indicated for diabetes, section should be done before term. The decision to perform early section will depend on several factors, among them, the outcome of previous pregnancies, the presence and severity of toxemia and the age and parity of the patient. The product of a pregnancy in an elderly and childless diabetic woman may justifiably be considered a "valuable baby," and every reasonable means taken to insure a successful outcome.

In the ten year period covered by this report the incidence of toxemia at Charity Hospital was slightly more than 10 per cent. Twenty-four of our 69 patients were toxemic and 1 eclamptic, to give an incidence of 35 per cent. But of the 24 babies, only 10 were lost, to give a fetal mortality of 41 per cent, as compared with 42 per cent mortality for the entire group. The patients with severe toxemias do, of course, have less chance of obtaining live babies, but in mild and moderate toxemia the fetal mortality is probably no greater than in diabetic patients without clinical evidence of toxemia (see fig. 3).

Nineteen, or 27 per cent, of the group of deliveries had obstetric complications other than toxemia and breech presentation. Vaginal bleeding occurred three times, premature separation of the placenta twice, polyhydramnios six times, premature rupture of fetal membranes five times and pyelonephritis three times, and obstetric difficulties due

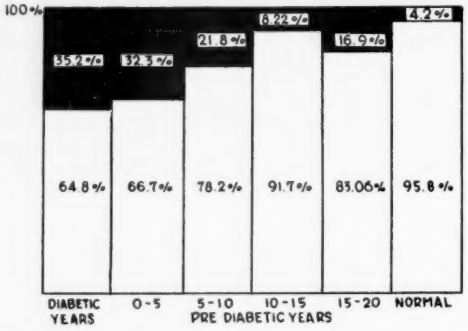

Fig. 5.—Percentages of live babies and fetal and neonatal deaths in pregnancies reaching term, based on figures in table 2. White spaces represent live births and black areas, fetal and neonatal deaths.

to the large size of the baby were noted six times. Obstetric complications are generally conceded to increase the incidence of fetal death,[5] but those noted in our series apparently did not do so, since fetal mortality in these patients was only 47 per cent, or slightly above the 42 per cent for all patients (see figure 3).

As in other series, the incidence of large babies was conspicuous in these patients. The average weight for the babies, 7.8 pounds (3,538 Gm.), is lowered by the lesser weight of the premature babies, and the fact that 8.4 per cent of the babies weighed more than 11 pounds (4,990 Gm.) gives a truer estimate of the situation. Concerning several of the patients data are available to show a progressive increase in the weight of babies during the years prior to the onset of the diabetes.

The excessive weight of the babies is due to splanchnomegaly and to abnormal amounts of fat and edema fluid. In the first few days of

life there is a rapid loss of weight due to elimination of fluid. Another common observation at autopsy is an exaggerated degree of erythropoiesis, and neonatal jaundice is frequently seen.

The theory is widely held that much of the neonatal difficulty of these babies is due to hypoglycemia, which results from hypertrophy of pancreatic islet tissue. The latter condition is not consistently seen, nor has it been possible to correlate its occurrence with hypoglycemia. However, hypoglycemia occurs so frequently that many pediatricians routinely administer glucose solution to the babies without concern for their blood sugar levels. White [2] abandoned the routine use of glucose solution on the very plausible theory that when administered needlessly it may act, in accord with Staub-Traugott effect, to produce hypoglycemia rather than to prevent it. White [8] was also of the opinion that insulin does not cross the human placenta and that the fear of administering insulin to the mother during labor because of its effect on the baby is unwarranted unless maternal hypoglycemia actually is produced. In fact, because of its stimulating effect on the fetal pancreas, maternal hyperglycemia may be more dangerous to the baby than maternal hypoglycemia. It is a common practice to abandon the use of insulin as the patient begins labor and to permit and even encourage hyperglycemia by the parenteral administration of glucose solution. While this plan certainly makes for easier and safer management of the mother, it may cause injury to the baby if carried to excess. The maintenance of moderate levels of blood sugar in the mother during labor, and the administration of glucose solution to the baby only when the blood sugar levels indicate the need for it, is probably optimum management.

No instance of fetal anomaly was observed, although malformations are said to occur more frequently in children of diabetic mothers.[8]

HORMONE IMBALANCE

For about fifteen years Smith and associates [9] tried to show that in patients with toxemia of pregnancy, and in some pregnant diabetic women with or without toxemia, there is an imbalance of ovarian and chorionic hormone levels. The information was extensively applied to diabetic patients by White,[7] and she and others were convinced that this is the one consistent factor to be found in those diabetic women who deliver stillborn babies or babies who die soon after birth. The diabetic women who were able to deliver live babies were observed to

8. White, P.: Pregnancy Complicating Diabetes: A Report of Clinical Results, J. Clin. Endocrinol. **3**:500 (Sept.) 1943.

9. Smith, O. W.; Smith, G. V. S., and Hurwitz, D.: The Relationship Between Hormonal Abnormalities and Accidents of Late Pregnancy in Diabetic Women, Am. J. M. Sc. **208**:25 (July) 1944.

have normal hormone levels. By substitution therapy with large doses of estrogen and progesterone, White was able to increase the rate of fetal survival from 50 to 90 per cent. Although these facts have been available for several years, the difficulty of performing animal assays and the cost of the hormone substances will continue to prevent their wide application. Smith and associates expressed the opinion that administration of large doses of diethylstilbestrol U. S. P. may sufficiently stimulate the production of progesterone to constitute adequate therapy. If this treatment proves adequate, it may be feasible to administer diethylstilbestrol, even without repeated hormone assays, to patients who clinically fall into the class which requires it.

Even without the aid of hormone therapy, it should be possible to manage diabetic pregnancies much more successfully than they commonly are handled. The chief means of so doing is the intelligent, though not routine, use of early section in those patients who seem to warrant it on the basis of previous pregnancies, severe toxemia and childlessness. Furthermore, the occurrence of the familiar pattern of large babies, toxemia and fetal or neonatal death should at once arouse the suspicion of the physician and detailed studies should be carried out to detect incipient diabetes. Even when the existence of diabetes cannot be established, it may not be far amiss to manage the patient according to the same principles which would apply to a woman with diabetes.

The problem of sterilization of diabetic women has at times been presented in consultation to the medical services. In this group of patients it was carried out only twice, once after severe eclampsia and once after repeated cesarean sections. We previously inferred that diabetes seldom, if ever, constitutes such a hazard to a woman that sterilization is required. Diabetes, though hereditary, is a recessive trait, and sterilization for eugenic reasons is hardly justifiable even if personal and public opinion would support it.

ILLUSTRATIVE CASES

Case 1.—This case illustrates the advantages of early and proper obstetric management. Diabetes first developed in a woman at the age of 14, and in her first pregnancy at 18 she delivered a child who died three days after birth. In subsequent pregnancies at 20 and 22 years of age she was delivered of living children by cesarean section. She was sterilized at the time of the second section, and thus escaped the danger and inconvenience of repeated, unsuccessful pregnancies. Possibly, determination of hormone levels during her first pregnancy might have foretold the outcome, so that section could have been used at that time. Some will feel that sterilization after a third section would have been more desirable, but at any rate this case illustrates the type of management which seems most desirable from the standpoint not only of fetal salvage but of reduction in maternal hazards.

Case 2.—In this woman diabetes developed at the age of 20. After spontaneous delivery of a normal baby when she was 22, she was permitted to deliver a series of

3 other babies, each of whom died within a few hours after birth. The patient is now 28 years old and has only 1 child in spite of bringing 4 pregnancies to term. She has moderately severe diabetes, and her pregnancies entail frequent episodes of acidosis and morbidity, as well as some risk to life. The case well demonstrates the fetal waste and maternal danger which may result from inadequate management.

CASE 3.—This patient was delivered of a stillborn child in her first pregnancy at 16 but obtained living children in subsequent pregnancies at 18, 19, 20 and 21 years of age, in spite of the fact that diabetes developed during the last pregnancy. Advocates of routine section would have little justification for applying the procedure in her next pregnancy.

SUMMARY

A review of all deliveries in diabetic and prediabetic (five years) women at Charity Hospital, New Orleans, over a ten year period is presented. Additional data were secured from obstetric histories taken from 148 women now active patients in the diabetic clinics of the same hospital.

Diabetic and prediabetic women were demonstrated to be as fertile as normal women. Their incidence of miscarriages was but little higher than estimates for normal women. The mortality and morbidity in the mothers were definitely greater than normal, but not sufficiently so to contraindicate pregnancy in diabetic women.

The insulin requirement frequently rose, and occasionally fell, but usually was little affected by the pregnancy. The fetal and neonatal mortality for those pregnancies brought to term during diabetic years was 35 per cent. The mortality progressively increased during the years before the onset of the diabetes and was significantly above normal for 20 years prior to the development of manifest diabetes.

Younger diabetic women have a better chance of delivering live babies than those over 35 years of age. The severity of diabetes exerts an adverse effect on fetal and neonatal mortality. Individual exceptions to this rule are frequent.

Premature delivery was frequent but resulted in live babies as frequently as when the pregnancy was brought to term. Except for an increased incidence of breech positions, the presentations and method of delivery were not unusual and did not significantly affect the outcome for the fetus. Early cesarean section is considered the surest method of obtaining live babies but is not advocated as a routine procedure.

The incidence of toxemia was three and one-half times that for nondiabetic women in the same hospital. Except in severe cases it contributed but slighly to fetal death. Obstetric abnormalities, other than toxemia, were more frequent than normal, but also accounted for but little of the increased fetal wastage. The occurrence of large babies was notable in diabetic and prediabetic years. Sterilization is seldom, if ever, needed on the indication of diabetes alone. Hormone imbalance, not studied in these patients, is discussed.

ANTIBODY RESPONSE IN PATIENTS WITH HYPOPROTEINEMIA

With Special Reference to the Effect of Supplementation with Protein or Protein Hydrolysate

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AND

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PHILADELPHIA

IMMUNITY is dependent in part on antibody production. There is ample evidence that antibodies are globulins modified in response to the presence of an antigen.[1] Antibody globulins, like other plasma proteins and body proteins as well, are derived from dietary protein and thus depend for their formation on protein intake adequate in quality and quantity.[2] Furthermore, the fundamental studies of Cannon and his co-workers[3] and of others[4] have shown that antibody production is lessened when hypoproteinemia is produced in experimental animals. Wissler and others[5] demonstrated that protein reple-

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1. Heidelberger, M.: Chem. Rev. **24**:323, 1939.

2. Schoenheimer, R.: J. Biol. Chem. **144**:541, 1942. Madden, S. C., and Whipple, G. H.: Physiol. Rev. **20**:194, 1940.

3. Cannon, P. R.; Chase, W. E., and Wissler, R. W.: J. Immunol. **47**:133, 1947. Cannon, P. R.; Wissler, R. W.; Woolridge, R. L., and Benditt, E. P.: Ann. Surg. **120**:514, 1944.

4. Berry, L. J.; Davis, J., and Spies, T. D.: J. Lab. & Clin. Med. **30**:684, 1945.

5. Wissler, R. W.; Woolridge, R. L., and Steffe, C. H., Jr.: Proc. Soc. Exper. Biol. & Med. **62**:199, 1946.

tion is associated with improved antibody response. The degree of protein depletion required to impair production of antibodies in animals was rather drastic in many of the experiments cited, and the relative importance of their observations as they relate to human antibody response has been challenged.[6]

Because of the clinical implications of these experimental studies, we have (1) investigated production of antibodies in hypoproteinemia in man, (2) tested the effect of increased dietary nitrogen intake on the formation of antibodies and other plasma proteins and (3) compared the effectiveness of a lactalbumin hydrolysate with that of a modified casein preparation.[7]

MATERIALS AND METHODS

Experiments with Protein Hydrolysate.—Forty-eight patients with hypoproteinemia were studied in the wards of the Philadelphia General Hospital. Each patient selected had a serum albumin level below 4 Gm. per hundred cubic centimeters, the lower limit of normal in our experience with the method used. Serum albumin was used instead of total protein as a criterion of protein deficiency because in many patients protein depletion may be masked by increased serum globulin resulting from infection, hepatic disease or other causes. The accompanying table shows the distribution of patients according to disease. The members of each group were treated as follows: Group AA received the standard hospital diet plus 80 Gm. of lactalbumin hydrolysate, equivalent to 59 Gm. of protein. Group AB were given the same diet and lactalbumin hydrolysate, but in addition they received typhoid inoculation. Group AC, patients receiving the hospital diet without supplementation, were likewise immunized with typhoid antigen and served as a control for Group AB.

Experiments with Modified Casein Preparation.—In a second series of 40 patients, 120 Gm. of a modified casein preparation equivalent to 74.5 Gm. of protein was administered daily (table). In addition, 14 persons in apparent

6. Schneider, H. A., in Harris, R. S., and Thiman, K. V.: Vitamins and Hormones, New York, Academic Press, Inc., 1946, vol. 4, p. 35.

7. The composition of the lactalbumin hydrolysate, aminonat,® as supplied by the manufacturer is as follows: The total nitrogen is 12 per cent; the protein equivalence (N × 6.25) is approximately 75 per cent, of which amino acids (amino acid N × 6.25) comprise 42.5 per cent. The average distribution of the important amino acids is as follows: arginine, 2.4 per cent; histidine, 1.75 per cent; lysine, 7.5 per cent; tryptophane, 1.27 per cent; phenylalanine 3.1 per cent; cystine, 1.8 per cent; methionine, 1.7 per cent; threonine, 4.2 per cent; leucine, 7.1 per cent; isoleucine, 5.7 per cent; valine, 4.7 per cent; glutamic acid, 9.6 per cent. The composition of the casein preparation, protinal,® is as follows: protein (N × 6.25) derived from milk, 61.25 per cent; carbohydrate (sugar lactose), 24 per cent. The distribution of the important amino acids is as follows: valine, 4.2 per cent; arginine, 2.4 per cent; histidine, 1.5 per cent; lysine, 4.2 per cent; tyrosine, 3.8 per cent; tryptophane, 1.0 per cent; phenylalanine, 3.5 per cent; cystine, 0.2 per cent; methionine, 2.1 per cent; serine, 3.6 per cent; threonine, 2.4 per cent; leucine, 7.0 per cent; isoleucine, 3.9 per cent.

good health with normal blood protein values (group PD) receiving the usual hospital diet without supplementation were studied chemically and immunologically. These served as controls.

Assignment of patients was made in such a way as to keep persons within each of the three groups roughly comparable to one another in regard to disease and its state, age, sex and other factors. Extremely ill patients were excluded. Statistical evaluation of the initial blood protein and typhoid titer values showed no significant differences between the groups. The usual medical care and medication for each patient, irrespective of the group to which he had been assigned, were maintained throughout the study. The standard hospital diet provided about 2,000 calories per day consisting of 70 Gm. of protein, 75 to 125 Gm. of fat and 150 to 250 Gm. of carbohydrate. Food was prepared under the supervision of dietitians [8] and was considered adequate with respect to the various nutrient factors. Records of food consumption were kept for each patient. The protein hydrolysate was administered twice daily as a "milk shake" prepared in a Waring blendor. Various flavoring substances were added, including sucrose, dextri-maltose® and vanilla extract. With few exceptions, the patients accepted

Distribution of Patients

Disease	Hydrolysate Group	Casein Group
Diabetes mellitus	17	16
Hepatic disease	11	6
Chronic pulmonary infection (not tuberculosis)	6	3
Anemia:		
Pernicious	2	3
Nutritional	3	6
Rheumatoid arthritis	6	5
Miscellaneous	3	1
Total	48	40

the quantity of hydrolysate in this form. Trials of larger amounts resulted in an occasional attack of diarrhea and impairment of appetite. The casein preparation was also administered in a milk vehicle. It was well accepted and tolerated. Milk employed in preparation of the protein supplements was that previously included in the patients' daily dietary allowance.

The patients were studied chemically and immunologically during a control period of seven to ten days. During the control and experimental period, blood specimens were collected twice weekly. Serum protein, albumin and globulin were determined by the Kingsley modification of the Howe method using 21.5 per cent sodium sulfate [9] for separation of albumin from globulin. Albumin determined by this method includes also much of the alpha globulins. However, this does not appreciably impair the significance of the findings in relation to the effects of nutritive state on serum albumin and the major portion of the globulin. Hemoglobin was estimated by the method of Evelyn [10] and plasma volume by means of the Evans blue dye method using 0.1 Gm. (in later

8. Misses Elizabeth Miller, Gloria Turner and Beth Farell, of the dietetic staff of the hospital, were of much assistance.

9. Kingsley, G. R.: J. Biol. Chem. **131**:197, 1939.

10. Evelyn, K. A.: Notes on Operation of the Evelyn Photoelectric Colorimeter, Philadelphia, Rubicon Co., 1943.

experiments, 0.2 Gm. of Evans' blue [11]); samples were then collected twenty, thirty and forty minutes after administration of the dye. Concentrations of dye were measured in a Beckman spectrophotometer at 620 millimicrons and were extrapolated to zero time for calculation of the plasma volume.

The antigen employed for immunization was a five hundred million suspension of Eberthella typhosa, thymol killed, and it was administered intracutaneously in 0.1 cc. amounts. This small amount was found to be sufficient to produce antibodies but gave no local or constitutional reactions. Injections were made at ten day intervals. At least two, and when possible three, injections were given. The agglutination titer was measured by using a standard commercial antigen (Lederle Laboratories, Inc.; prepared by the Welch and Stuart [12] method) and diluted to approximately five hundred million organisms per cubic centimeter. Tests were performed by making serial twofold dilutions (1:10 to 1:1,280) of the patients' serum followed by the addition of a constant volume of antigen. The tubes were incubated at 50 C. for a half hour, centrifugalized and read immediately. A reading was regarded as positive when a definite agglutination occurred, 3 or 4 plus in a given tube; weaker reactions were ignored in the final analysis. During the control period, i. e., prior to antigen stimulation and/or the use of supplementation, the typhoid titers were measured and found to average less than 1:5.

RESULTS

Antibody Response in Groups Receiving Hydrolysate.—Both AB and AC groups responded to injection of the typhoid antigen with a rise in H antibody titer (fig. 1). The O antibody titer was less pronounced and too variable to warrant detailed discussion; therefore the data presented give only the H antibody titer. During the ten days after the initial injection the average titer in the two groups had increased to approximately the same extent. After the second immunizing dose (the tenth day) patients in group AB showed a continuing rise in titer, while the average agglutination titer in group AC was less pronounced. A third immunizing dose was followed again by a greater rise in group AB. The antibody response was studied for thirty days. It is significant that the average titers at the time of each of the six consecutive measurements following the initial rise were consistently higher in group AB than in group AC. As anticipated, the control group AA, receiving protein hydrolysate as a supplement to the diet but without antigen stimulation, showed the same antibody titer as during the control period.[13]

Antibody Response in Groups Receiving Casein Preparation.—Subjects in groups PB receiving the casein preparation responded to antigenic stimulation in a way comparable to that observed in the amino

11. Gibson, J. G., and Evans, W. A.: J. Clin. Investigation **16**:361, 1937.

12. Welch, H., and Stuart, C. A.: J. Lab. & Clin. Med. **21**:411, 1936.

13. Hyman Menduke of the Wharton School, University of Pennsylvania, made the statistical analysis of the data.

acid hydrolysate group (fig. 2). The response was less pronounced than in the hydrolysate series. This difference in response between the casein and hydrolysate-supplemented groups was more apparent than real, as will be pointed out in the discussion. It is important to note that persons in group PD with normal serum protein levels showed a significantly higher antibody value than persons in group PB or PC.

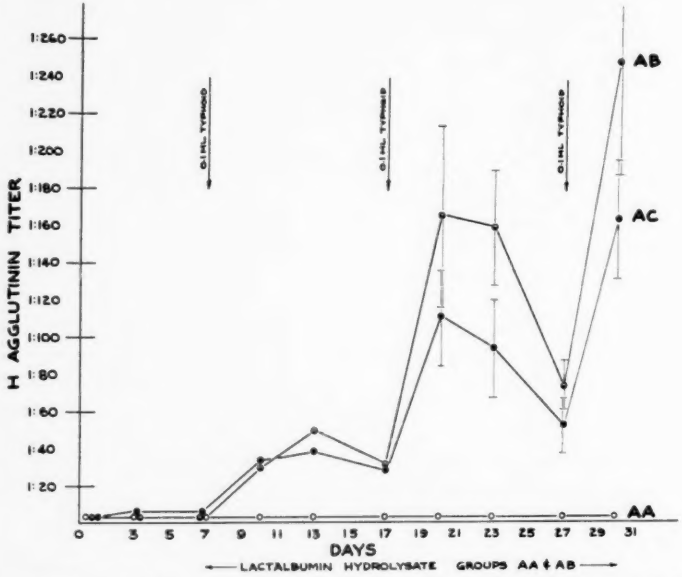

Fig. 1.—Antibody response after three injections with typhoid. Group *AA* was not immunized and shows no change in antibody titer. Group *AB* (supplemented) shows a greater response than group *AC* (nonsupplemented). The difference between groups *AB* and *AC* becomes more apparent after the second and third typhoid inoculation. The light perpendicular lines at points representing the twentieth and thirtieth days show the standard errors of the means.

Blood Protein Changes in Groups Receiving Hydrolysate.—A small rise in serum globulin occurred in group AB at the time of the initial antibody response to injection of typhoid antigen. A second and third injection of typhoid antigen caused smaller increases in globulin after the previous gains had been dissipated. These increases coincided with the rise in antibody titer. No obvious change in globulin concentration occurred in groups AA and AC.

Serum albumin concentrations increased in groups AA and AB receiving supplementation with protein hydrolysate (fig. 3). Although the gains were small, they were statistically significant. Total protein

concentrations showed an upward trend in all three groups. Cyclic changes in total protein in group AB were related to typhoid injections and paralleled the globulin changes.

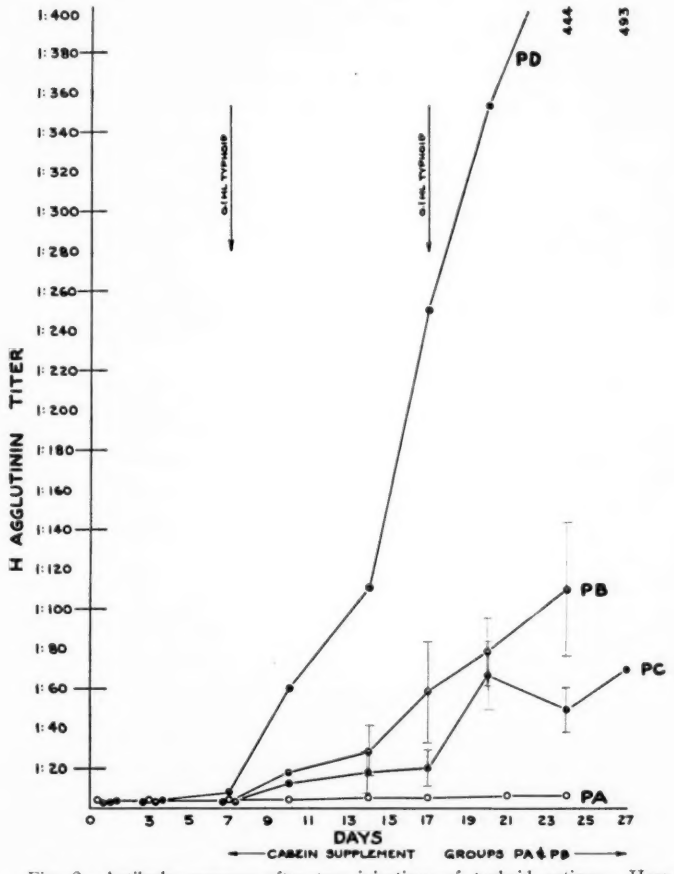

Fig. 2.—Antibody response after two injections of typhoid antigen. Here again the casein-supplemented group *PB* shows a higher response than group *PC*. The light perpendicular lines at points representing the fourteenth day onward show standard errors of the means. Group *PD*, with normal serum protein concentration, shows a response greatly exceeding that in the hypoproteinemic patients.

Hemoglobin: The concentrations of hemoglobin increased an average of 1 Gm. per hundred cubic centimeters in group AA during

the experimental period—a significant rise. By contrast, group AB showed downward trends, with variable values (fig. 4), while group AC showed no obvious changes.

Plasma and Blood Volumes: Plasma volumes were higher at the end of the treatment period in groups AA and AB and unchanged in group AC. Blood volumes increased in all groups. Because only a portion of the patients were tested and the observed changes were not statistically significant, further comment will be omitted.

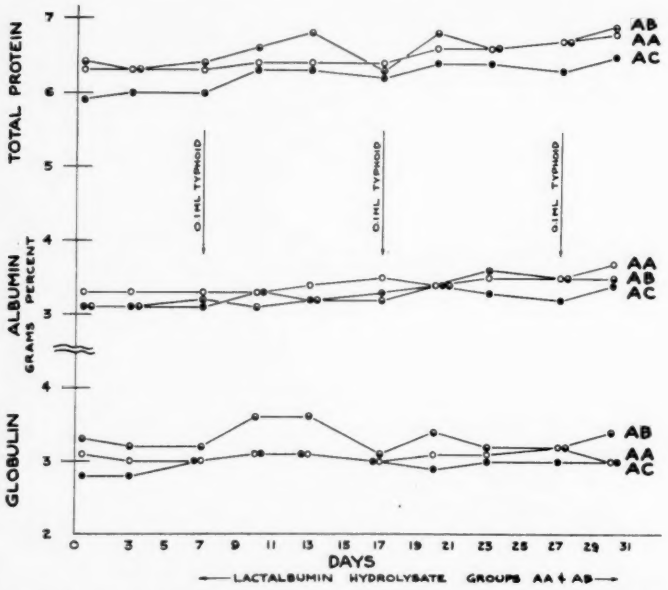

Fig. 3.—Serum protein response in the hydrolysate-supplemented groups *AA* and *AB* as compared with the response in the unsupplemented group *AC*. Total protein and albumin concentrations showed an upward trend in all three groups. There was a small increase in globulin in group *AB* coinciding with the typhoid inoculations.

Blood Protein Changes in Groups Receiving Casein Preparation.—All the hypoproteinemic patients in this series showed a rising trend in the total serum protein. The rise was somewhat greater in the nonimmunized group PA.

Group PD (normal blood protein values and without supplementation), on the contrary, showed a slight downward trend.

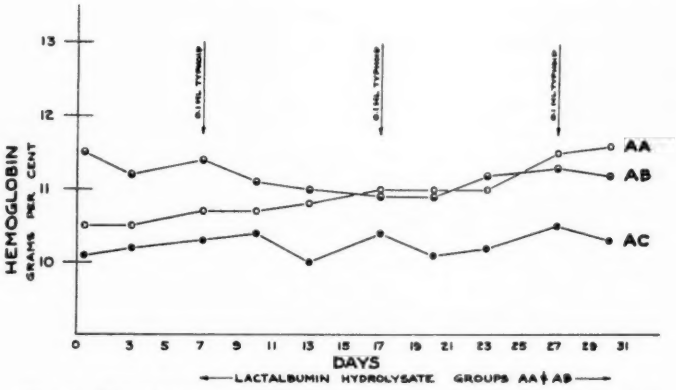

Fig. 4.—Hemoglobin concentrations in the hydrolysate-supplemented group *AA* shows a significant increase, while in group *AB* there is a downward trend. Group *AC* shows no definite trend.

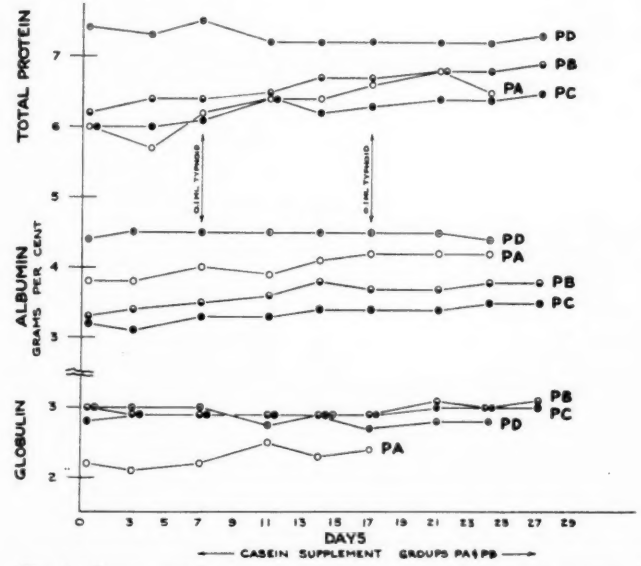

Fig. 5.—Serum protein response in the casein-supplemented groups *PA* and *PB* as compared with that in the nonsupplemented group *PC*. The total serum protein and the albumin are increased in all three groups of the hypoproteinemic patients. The rise in globulin is not significant. Changes in group *PD* are not significant.

Albumin: Again, a slight increase in albumin values occurred in the hypoproteinemic subjects, with little difference between the groups. Subjects in group PD showed no change.

Globulin: In group PA there is an upward trend in globulin, which, however, is not significant. In groups PB and PC there is no obvious change. In group PD there is a slight but nonsignificant decrease in values despite the pronounced antibody response (fig. 5).

Hemoglobin: The hypoproteinemic groups showed a slight rise in hemoglobin concentration. On the other hand, group PD showed no change (fig. 6).

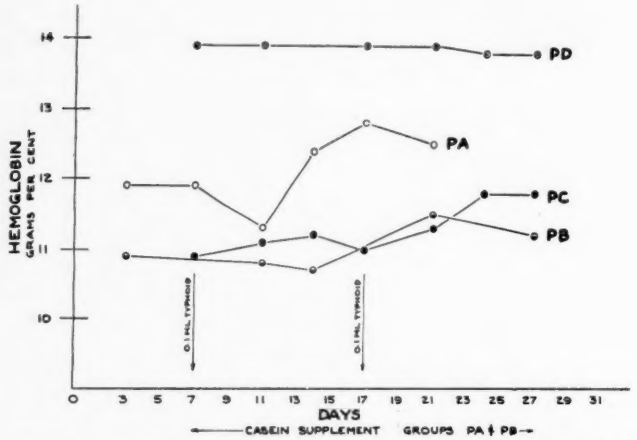

Fig. 6.—Hemoglobin concentrations in the hypoproteinemic patients in the casein-treated series show an upward trend. Group *PD* shows no change.

COMMENT

It is important to emphasize that the patients whose antibody response in relation to dietary supplementation was studied were suffering from various diseases. It is possible that each disease may influence production of antibodies without reference to dietary factors. However, an attempt was made to eliminate specific diseases as variables by allocating a similar number of cases of each disease to each group. Furthermore, a common factor present in all was hypoproteinemia, and it is significant that in those groups receiving supplementation with antigen stimulation production of antibodies was increased as compared with those who received no supplementation. Additional support for the importance of protein nutrition in relation to production of antibodies is provided by the striking antibody response in

persons with normal blood protein levels. The antibody response exceeded by far that of the hypoproteinemic patients who received supplementation.

Several factors account for the initially abnormal blood protein pattern in the patients studied. In some the disease per se (e.g., cirrhosis of the liver) was sufficiently pronounced to account for the hypoproteinemia. In others decreased protein intake and/or increased protein loss were outstanding factors.

Patients with diabetes mellitus showing hypoalbuminemia commonly had complications such as osteomyelitis or varying degrees of gangrene of the lower extremitites. Retinopathy was present in about 90 per cent of the diabetic patients. Catabolic loss of nitrogen, due to various causes, is probably an important factor in the hypoalbuminemia in diabetes with complications. Hepatic dysfunction did not appear to contribute to the hypoalbuminemia in the diabetic group. The point of view has been advanced recently that in trauma or infection the increased loss of nitrogen may be associated, among other factors, with an increased urinary excretion of adrenal corticoids.[14] It is conceivable that such an endocrine-protein interrelationship may partly explain the increased nitrogen loss and increased gluconeogenesis in diabetes mellitus with complications. However, this hypothesis requires experimental proof.

In the patients suffering from chronic pulmonary infections a loss of protein, due to expectoration, contributed to protein depletion. Co Tui and others[15] have shown that nitrogen loss in exudates can be large.

No specific explanation is offered for the hypoalbuminemia observed in patients with arthritis; undoubtedly, numerous factors are involved, including low grade fever and the metabolic disturbances incident to restricted activity. General malnutrition was observed in 9 patients of the group with anemia.

The rate of protein repletion was variable. The patients in the diabetic group showed a slow return toward normal protein levels; in general, the rise in the blood protein values paralleled the clinical improvement of the complication. This is in harmony with the observations of Lewis and others,[16] who reported that low albumin

14. Shipley, R. A.; Dorfman, R. I.; Buchwald, E., and Ross, E.: J. Clin. Investigation **25**:673, 1946. Albright, F., in Harvey Lectures, Lancaster, Pa., Science Printing Company, 1943, vol. 38, p. 123.

15. Co Tui: Bull. New York Acad. Med. **21**:631, 1945.

16. Lewis, L. A.; Schneider, R. W., and McCullagh, E. P.: J. Clin. Endocrinol. **4**:535, 1944. Schneider, R. W.; Lewis, L. A., and McCullagh, E. P.: Am. J. M. Sc. **212**:462, 1946.

levels in cases of diabetic retinitis were slow to return to normal even after the protein intake was increased by 20 to 60 Gm. daily.

Our experience is in accord with the observation of others that when the low level of blood proteins is due to defective synthesis, as in disease of the liver, the administration of additional protein does not by itself correct the abnormal blood protein pattern [17] although clinical improvement may occur.

In support of this, certain patients, especially those with cirrhosis, showed an increased antibody titer after supplementation. On the other hand, when the hypoalbuminemia is not directly associated with an intrinsic failure of protein synthesis, a favorable response can be expected. To illustrate, patients with anemia incident to malnutrition showed a definite improvement of the plasma protein pattern.

In the early period of our studies it became apparent that many of our patients were receiving an inadequate caloric intake. Thus it became essential to increase the intake of food to prevent loss of weight and diversion of amino acids to production of energy. We found that an average of 2,000 calories per day was sufficient for this purpose. It is well known that in animals and patients there is an impairment of protein utilization for tissue synthesis when caloric intake is restricted.[18] In this connection we wish to emphasize again that hospital patients are frequently on a low intake not only of protein but of total calories.[19]

For effective production of antibodies it is necessary to restore protein reserves; if the capacity for protein synthesis is not defective, repletion and improved production of antibodies may be expected.

Our patients in groups AB and PB receiving protein supplements showed, on the average, a higher antibody response to typhoid antigen than did those in groups AC and PC similarly treated without protein supplementation. It is interesting to note that the difference became pronounced ten days after inoculation. At this time the tissues apparently accumulated sufficient supply of protein for antibody synthesis. This observation is in accord with the work of Wissler and others,[20] who found that a short interval (two days) of protein repletion in hypoproteinemic animals was insufficient to supply amino acids for optimum synthesis of antibodies.

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17. Barr, D. P.: Am. J. Med. **3**:478, 1947.

18. (*a*) Benditt, E., and others: J. Lab. & Clin. Med. **33**:257, 1948. (*b*) Cannon, P. R., in Anson, M. L., and Edsall, J. T.: Advances in Protein Chemistry, New York, Academic Press, Inc., 1945, vol. 2.

19. Duncan, G.: Philadelphia Med. **43**:769, 1948. Co Tui.[15]

20. Wissler, R. W.; Woolridge, R. L.; Steffee, C. H., Jr., and Cannon, P. R.: J. Immunol. **52**:267, 1946.

Although the antibody response in patients whose diets were supplemented with the casein preparation was less pronounced, it should be noted that this series of patients in general failed to respond to the same extent. Thus the control group PC did not respond as well as the control group AC. The reason for the difference between the agglutinin titers in the two series of patients is not known. Since each series is fully controlled, the difference should not affect the conclusions concerning the comparative value of the two products used. Actually when the areas under the curves are compared in the two series, the percentage improvement observed in the groups whose diets were supplemented is substantially alike. In other words, the cumulative antibody response is about the same. In this connection it may be mentioned that Mueller and Cox [21] found no significant difference in the nutritive value of casein as compared with lactalbumin.

The control group PD with normal blood protein levels showed the best antibody response, even though they received no protein supplementation. Our results are in agreement with the work of Cannon and others,[22] who demonstrated a much greater output of typhoid agglutinins in well fed rabbits than in protein-depleted animals. Furthermore, this confirms the value of a good nutritive state in relation to immune mechanisms, as previously emphasized.[23] None of the patients studied received salicylates. These are said to impair significantly production of antibodies.[24]

The mechanism by which protein repletion affects formation of antibodies is not known. That the amino acids are incorporated into the body's protein "pool" and are made available for protein requirements of the organism, including formation of antibodies, is likely on the basis of feeding experiments with isotopic amino acids in actively immunized rats and rabbits (Schoenheimer and others [25]). They showed that antibodies, like serum and body proteins, participate in metabolic reactions involving the uptake of dietary nitrogen. The dynamic equilibrium among food, plasma and tissue proteins has already been emphasized by Whipple and his colleagues.[26]

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21. Mueller, A. J., and Cox, W. M., Jr.: Science **105**:508, 1947.

22. Cannon, P. R.; Chase, W. E., and Wissler, R. W.: J. Immunol. **47**:133, 1943.

23. Rose, S. B.; Rose, W. B., and Kolmer, J. A.: J. Infect. Dis. **59**:50 and 174, 1936.

24. Jager, B. V., and Nickerson, M.: Am. J. Med. **3**:408, 1947.

25. Schoenheimer, R.; Ratner, S.; Rittenberg, D., and Heidelberger, M.: J. Biol. Chem. **144**:541, 1942.

26. Holman, R. L.; Mahoney, E. B., and Whipple, G. H.: J. Exper. Med. **59**:269, 1934.

Recent evidence published by Ehrich and Harris,[27] Dougherty, Chase and White[28] and Kass[29] indicates that lymphoid cells contain gamma globulin and that they are concerned in formation of antibodies. Apparently members of group PD had sufficient protein reserves, and presumably members of groups AB and PB were provided with sufficient nitrogen by supplementation to support a higher rate of antibody production. The poor response observed in groups AC and PC is in harmony with the observations of Kuszynski,[30] who in a classic paper showed that malnutrition was accompanied with involutions of lymph nodes; on the other hand, animals fed protein-rich food ad libitum showed lymphoid hyperplasia, with rapid increase in weight of lymph nodes. Essentially similar conclusions were arrived at by Jackson.[31]

Our results are not in agreement with those reported by Metcoff and others.[32] However, it should be noted that Metcoff employed a viable pathogen in the susceptible rat whereas our data were obtained by the use of a relatively mild, nonviable antigen in man.

Bieler and his associates[33] failed to note a significant lowering in circulating antibodies in chronic malnutrition. Our observations are not strictly comparable to those of Biehler, whose studies were concerned with natural immune factors.

Hemoglobin.—Hemoglobin changes show that supplementation with hydrolysate causes a favorable response, as illustrated by a significant rise in group AA. During active immunization, members of groups AB and AC failed to reveal a significant change in hemoglobin value. On the other hand, supplementation with casein had no specific effect on hemoglobin regeneration, since members in group PC showed a somewhat larger increment in hemoglobin than members in groups PA and PB.

SUMMARY AND CONCLUSIONS

Patients with various diseases were studied for antibody response in relation to dietary supplementation. A common factor present in all

27. Ehrich, W. E., and Harris, T. N.: J. Exper. Med. **76**:335, 1942; Science **101**:28, 1945.

28. Dougherty, T. F.; Chase, J. H., and White, A.: Proc. Soc. Exper. Biol. & Med. **57**:295, 1944.

29. Kass, H.: Science **101**:337, 1945.

30. Kuszynski, M. H.: Virchows Arch. f. path. Anat. **239**:185 and 302, 1922.

31. Jackson, C. M., cited by Cannon, [18b] p. 1042.

32. Metcoff, J., and others: J. Lab. & Clin. Med. **33**:47, 1948.

33. Bieler, M. M.; Ecker, E. E., and Spies, T. D.: J. Lab. & Clin. Med. **32**:130, 1947.

was hypoalbuminemia. A total of 102 subjects were studied immunologically and chemically.

Fifty-three patients received nitrogen supplementation in the form of a lactalbumin hydrolysate or a modified casein preparation. The following conclusions appear to be warranted:

1. Patients with disturbance of protein metabolism sufficient to cause low serum albumin show an appreciable impairment of production of antibodies.

2. Supplementation with lactalbumin hydrolysate or casein preparation enhances formation of antibodies and partially overcomes the subnormal response in patients with hypoalbuminemia. However, the improvement in antibody response fails to attain the high titer observed in subjects with normal blood protein values receiving the same antigenic stimulation.

3. Supplementation with protein or lactalbumin hydrolysate increases the average blood protein values moderately in some instances and in others has no effect.

4. The modified casein preparation appears to be as effective as the lactalbumin hydrolysate in restoring production of antibodies.

Technical assistance was given by Mrs. Josephine Clough and Miss Marian Brenman.

ABSTRACT OF DISCUSSION

Dr. Paul R. Cannon, Chicago: These observations by Dr. Wohl and his group are significant. They demonstrate in man the same correlation between protein deficiency and reduced antibody production which has been found in lower animals, particularly the rat and the rabbit. They illustrate also the problem of the relation of the degree of protein deficiency to impaired antibody formation. It is striking that even with relatively mild degrees of protein deficiency, such as is shown in the patients they studied, depressed antibody formation was demonstrable. In the more severe degrees of protein deficiency one should expect an even greater impairment of antibody fabrication, as in the case with other types of body protein synthesis. The problem of antibody production and utilization is emphasized by this work in relation to both the quantity and the rate of production and the quantity and rate of utilization. It is known that relatively high degrees of resistance can be obtained with a relatively low antibody titer but that circulating antibody can be combined with and its concentration reduced in the presence of an advancing infection.

Dr. Wissler in our group has shown with protein-deficient rats that when they are immunized in the same manner as well nourished rats by injection with a pneumococcic vaccine and then challenged with an infective dose the former cannot localize the pneumococci in the local lesion as effectively as can the latter.

Lastly, the question of protein repletion by supplementation with protein hydrolysates illustrates the complicated nature of the problem. Dr. Wohl emphasized the importance of calories. The problem of antibody fabrication presumably is but a part of the larger problem of protein synthesis, and accumulating evidence indicates that several elements are concerned, including structural units, the amino acids that go into the proteins, and activating units, the enzyme systems, vitamins, minerals and calories. When the caloric intake is adequate, the vitamin intake adequate and the structural units supplied, one would expect, as these experiments have shown, a more effective synthesis of antibodies and a more effective acquired resistance.

ELECTROLYTE COMPOSITION OF SWEAT

Clinical Implications as an Index of Adrenal Cortical Function

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ANN ARBOR, MICH.

DURING the past fifteen years a large number of steroid compounds have been isolated from adrenal cortices of animals. Whether the adrenal cortex during life actually secretes each of these steroids remains an unsolved problem. In more recent years it has gradually become apparent that if one classifies according to their major functional effects the various physiologically active steroids which have been derived from the adrenal gland each falls into one of three main groups:

(1) Adrenal steroids possessing activities of sex hormones
  (*a*) Androgenic
  (*b*) Estrogenic
  (*c*) Progesterone

(2) Adrenal steroids which affect protein, carbohydrate and uric acid metabolism and which also produce important hematologic changes.

(3) Adrenal steroids which act mainly on sodium, potassium and chloride metabolism and, thus, on water metabolism as well.

Even when classified according to their major functional activities, certain of the steroids exhibit important physiologic effects in one or both of the other two fields. The androgenic adrenal steroids affect, either directly or indirectly, both protein and electrolyte metabolism. Those corticosteroids which produce their primary effects on protein, carbohydrate and uric acid metabolism show, in addition, secondary effects on electrolyte metabolism.

On the other hand, desoxycorticosterone, one of the steroids found in the gland in small amounts (and the one most readily synthesized) affects electrolyte metabolism only. It has no sex-hormone-like activity

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and has been shown to have no effects on protein, carbohydrate or uric acid metabolism. Neither does it affect the cellular elements of the blood. It is possible that the adrenal cortex produces steroids other than desoxycorticosterone which also have their primary effect on electrolyte metabolism. Whether these might have, in addition, an effect in the other two spheres is unknown. The fact remains, however, that it is possible to show intense changes in electrolyte metabolism with the use of desoxycorticosterone without producing any changes related to the other known functions of the adrenal cortex. Means presently available for measuring in human beings the activities of the three main types of corticosteroids are classified in the accompanying table.

Present Means of Measuring Activities of Corticosteroids

I. Steroids possessing activities of sex hormones
  1. Urinary excretory products
    (a)* 17-ketosteroids (androgenic). Chemical colorimetric and biologic assay
    (b)* Estrogenic substances. Biologic assay and chemical colorimetric
  2. Metabolic effects
    (a) Protein anabolic—not clinically useful
II. Steroids which affect protein and carbohydrate metabolism
  1. Urinary excretory products
    (a)* "11-oxysteroids." Biologic assay and chemical colorimetric
  2. Metabolic effects
    (a) Protein catabolic (or antianabolic)—not clinically useful
    (b) Blood sugar effects
      (1) Increased with excessive steroid producton } nonspecific
      (2) Decreased with diminished steroid production } nonspecific
      (3) Insuln sensitivity tests } nonspecific
  3. Acute effects of stimulation with pituitary adrenocorticotropin
    (a) Increased urinary content of uric acid } for testing cortical
    (b)* Sharp fall in circulating eosinophile cells } hypofunction
III. Steroids which possess a desoxycorticosterone-like effect
  1. Urinary excretory products—no method available
  2. Metabolic effects
    (a) Renal reabsorption of sodium, potassium and chloride
      (1)* Sodium chloride restriction tests in cortical hypofunction } Dangerous
      (2)* Potassium tolerance tests in cortical hypofunction } Dangerous
      (3) Tests of speed of water diuresis in hypofunction (not dependent entirely on "salt-active" steroids)
      (4) No test for hyperfunction

* Good index.

In several clinical syndromes known to be associated with abnormal adrenal cortical function it has been shown, by the means indicated in the table, that a high degree of correlation exists between clinical manifestations, metabolic aberrations and the amount and type of excretory steroids found in the urine. To date, all these methods, either chemical or biologic, give an index of adrenal cortical function with respect only to those steroids which possess activities of sex hormones or to those which affect the metabolism of protein, carbohydrate and uric acid. No simple method is available which will indicate changes in the production of those corticosteroids which affect primarily the movement of electrolytes and water throughout the body.

A relationship in normal persons between adrenal cortical function and the concentrations of sodium and chloride in sweat has been

reported in previous communications.[1] The present one deals mainly with observations made on patients suffering from a variety of endocrine disorders involving abnormal function of the adrenal cortices.

COLLECTION OF SAMPLES OF SWEAT

A simplified, standardized method for collection of samples of sweat will be reported at a later date. The present data were obtained from samples collected during a two hour resting exposure of the whole body to humid heat (95 F. and 90 per cent relative humidity). Samples from the hand and forearm were obtained in rubber gloves, the ends of which were sealed, above the elbows, to the cleansed, dried skin before exposure to heat. Samples from various other skin sites were obtained simultaneously by the method pictured in figure 1. Here

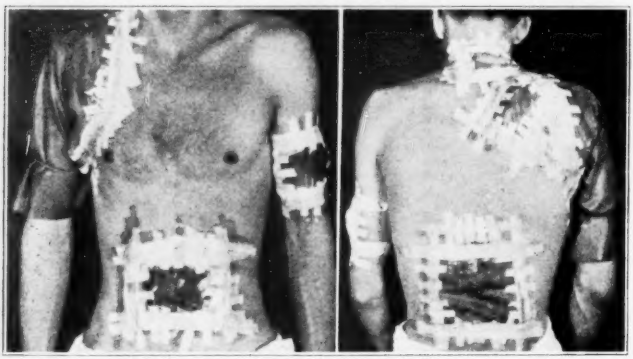

Fig. 1.—Collection of samples of sweat.

an electrolyte-free piece of absorbent cotton is placed beneath the rubber dam, and the latter is sealed to the dried skin. Another larger square of rubber is then sealed outside the first one for added protection against a leak. At the end of the period of exposure to heat the cotton (partially or completely saturated with sweat) is picked up

1. (*a*) Conn, J. W., and Johnston, M. W.: The Function of the Sweat Glands in the Economy of NaCL Under Conditions of Hard Work in a Tropical Climate, J. Clin. Investigation **23**:933 (Nov.) 1944. (*b*) Conn, J. W.; Johnston, M. W., and Louis, L. H.: Acclimatization to Humid Heat: A Function of Adrenal Cortical Activity, ibid. **25**:912-913 (Nov.) 1946. (*c*) Conn, J. W.: The Mechanism of Acclimatization to Heat, in Dock, W., and Snapper, I.: Advances in Internal Medicine, New York, Interscience Publishers, Inc., 1949, to be published. (*d*) Conn, J. W.; Louis, L. H.; Johnston, M. W., and Johnson, B.; The Electrolyte Content of Thermal Sweat as an Index of Adrenal Cortical Function, J. Clin. Investigation **27**:529-530 (July) 1948.

with an electrolyte-free forceps and transferred immediately to an air-tight weighing dish. After weighing, an exact amount of distilled water (10 to 20 cc.) is added to the dish. Next, the cotton and water are mixed sufficiently to insure equal concentrations of electrolytes in the cotton and the surrounding fluid. The fluid is analyzed. The cotton is dried to constant weight, the difference between this and its first wet weight representing the weight of the sweat sample. From these data the concentration of electrolytes in the sweat sample is easily obtained. Known concentrations of sodium and chloride added to absorbent cotton and then determined by the procedure described yield results with less than 1 per cent error.

Sodium content was determined by the method of Butler and Tuthill [2] and chloride content by the Harvey modification of the Volhard method.[3]

RESULTS

Figure 2 shows graphically the effect of desoxycorticosterone acetate (DCA) and of purified adrenocorticotropic hormone (ACTH)[3a] on the concentrations of sodium and chloride in the sweat of 6 normal persons. Note that both substances produce a similar, great decrease in the sweat content of sodium and chloride. Since adrenocorticotropic hormone is ineffectual in the absence of the adrenal cortices, the conclusion is valid that it has stimulated the production of desoxy-like corticosteroids. Indeed, under these same conditions a tremendous renal retention of sodium and chloride occurs together with a diuresis of potassium.[1c] However, the renal effect is evanescent while the sweat continues to reflect the desoxycorticosterone effect for as long as either material (desoxycorticosterone acetate or adrenocorticotropic hormone) is administered.[1c]

Subjects 1, 2 and 3 have initial values for sweat sodium and chloride in the high normal range, and the responses to both substances are similar. Adrenocorticotropic hormone, however, also increases production of androgenic steroids, as shown by the marked increase in urinary 17-ketosteroids (compare subjects 1 and 3).

Subjects 4, 5 and 6 gave the lowest initial values for sweat sodium and chloride of all normal subjects studied (22). This we take to indicate a higher (but still physiologic) degree of adrenal cortical activity than is present in most normal persons. It is significant that

2. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J. Biol. Chem. **93**:171-180 (Sept.) 1931.

3. Harvey, S. C.: The Quantitative Determination of Chlorides in the Urine, Arch. Int. Med. **6**:12-18 (July) 1910.

3a. Dr. J. R. Mote, The Armour Research Laboratory, Armour and Company, Chicago, Ill., provided the purified adrenocorticotropic hormone used in these studies.

when the adrenals of these subjects were stimulated with adrenocorticotropic hormone the concentrations of sweat sodium and chloride fell to levels which we have observed only in cases of adrenal cortical cancer or of Cushing's syndrome (figs. 4 and 7). Similarly, the excretion of urinary 17-ketosteroids in subjects 5 and 6 rose into the range frequently observed in cases of adrenal cortical cancer.

Note that in all except subject 3 both desoxycorticosterone acetate and adrenocorticotropic hormone, in addition to decreasing the concentration of sodium and chloride in sweat, reversed the normal relationship of sodium to chloride. Thus, under the influence of a pronounced desoxy-like effect the tubules of the sweat glands reabsorb more sodium than chloride. This same phenomenon occurs in the renal tubules but is relatively transitory.[1c] The same sweat pattern

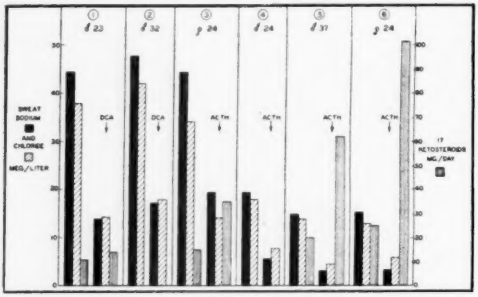

Fig. 2.—Effect of desoxycorticosterone acetate and of adrenocorticotropic hormone on sweat sodium and chloride and on urinary 17-ketosteroids.

(low concentration, with reversal of the normal sodium and chloride relationship) has been observed on numerous occasions in patients suffering from excessive functional activity of the adrenal cortex.

Figure 3 shows the results of detailed studies in cases of Addison's disease. The values for sodium and chloride of sweat in the untreated state are much higher than the highest normal values yet encountered. The effects of treatment (desoxycorticosterone acetate or lipoadrenal cortex® [The Upjohn Company]) and of cessation of treatment are clear. Our observations on well controlled cases of Addison's disease show that the levels of sodium and chloride in sweat fall into the normal range. One patient with Addison's disease admitted to the hospital with severe desoxycorticosterone acetate intoxication showed abnormally low concentrations of sweat sodium and chloride. Thus, sweat sodium and chloride values are not only of diagnostic value in conditions associated with increased or decreased activity of the

desoxy-like steroids but are valuable in judging proper control of electrolyte metabolism in cases of treated Addison's disease.

Figure 4 demonstrates the results obtained in 3 patients suffering from excessive adrenal cortical function. All 3 had an abnormally great urinary excretion of 17-ketosteroids but presented different

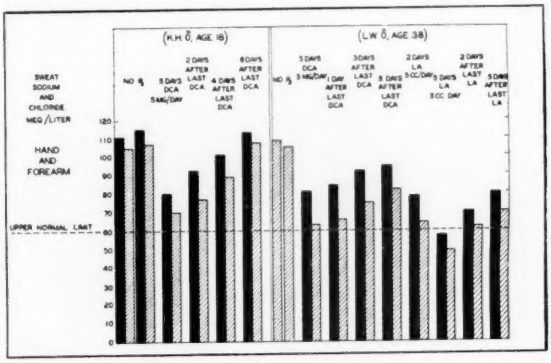

Fig. 3.—Effect of desoxycorticosterone acetate and of lipoadrenal (*LA*) on sweat sodium and chloride in Addison's disease.

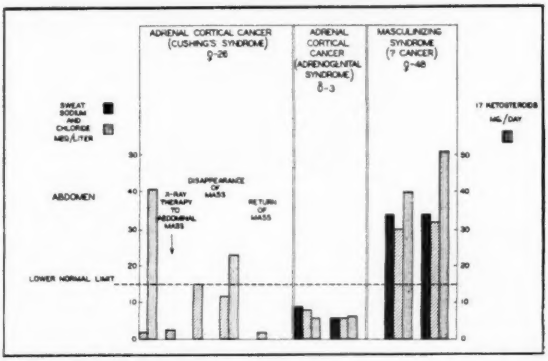

Fig. 4.—Relation of desoxy-like steroid activity to 17-ketosteroid excretion in hyperadrenal syndromes.

clinical syndromes. B. H. and D. B. were proved to have carcinomas of the cortex of the adrenal gland. L. N. had an androgen-producing tumor within the right ovary.

In B. H. the occurrence was typical of Cushing's syndrome. Although production of androgenic corticosteroids (protein anabolic)

was excessive as indicated by the high level of urinary 17-ketosteroids, the presumption is valid, in view of the syndrome presented, that production of "11-oxysteroids" (protein catabolic or antianabolic and blood sugar raising) was relatively greater than the production of androgenic corticosteroids.[4] Levels of chloride in the sweat in this case (1.7, 3.3, 2.7, 2.2, 2.7 and 2.2 milliequivalents) were the lowest that we have obtained in any circumstances in the course of analyzing

Fig. 5.—Typical adrenogenital syndrome.

over 3,000 samples of sweat. B. H., then, gave evidence of excessive production of all three types of adrenal corticosteroids. As indicated in figure 4, temporary disappearance of the mass in the left flank, following roentgen ray therapy, was associated with a fall in urinary excretion of 17-ketosteroids and with a rise in the concentration of chloride in the sweat. The patient's final admission to the hospital disclosed a return of the mass. The sweat chloride had returned to its former low level. Urine for determination of 17-ketosteroids was not obtained.

4. Venning, E. H., and Browne, J. S. L.: Excretion of Glycogenic Corticoids and of 17-Ketosteroids in Various Endocrine and Other Disorders, J. Clin. Endocrinol. **7**:79-101 (Feb.) 1947.

Figure 5 indicates the typical adrenogenital syndrome presented by D. B. For his age, the excretion of 17-ketosteroids was three to four times the normal. The clinical picture was one of excessive androgenic activity and increased muscular development (protein anabolic effect). Carbohydrate tolerance was normal. Production of "11-oxysteroids" may or may not have been excessive in this case. If it was increased, the preponderant activity was being exerted by the androgenic steroids. The levels of sodium and chloride in the sweat indicate that desoxy-like steroids, too, were being produced in excess.

Thus, in the 2 cases of proved carcinoma of the adrenal gland evidence of increased activity of the desoxy-like corticosteroids was obtained. This does not mean, necessarily, that in all cases of adrenal cortical cancer excessive amounts of the steroids that affect electrolyte metabolism will be produced. Patient L. N., shown in figure 6, presented the most intense picture of virilization which we have encountered in a female. Urinary 17-ketosteroids were abnormally high and evidence of androgenic excess was evident in the virilization and in the tremendous muscular development (protein anabolic effect) which began with the onset of profuse hirsutism and amenorrhea. Carbohydrate tolerance was normal. The concentrations of sodium and chloride of the sweat were well in the normal range and indicated that desoxy-like corticosteroids were not being produced in excess. In this case it seems reasonable to conclude that the excessive activity was limited to the production of abnormally large amounts of androgenic steroids. That this conclusion is not unequivocal is recognized.[5]

In figure 7 are shown comparative levels of sweat sodium and chloride in normal persons and in cases of the various well recognized clinical dysfunctions of the adrenal cortex. It must be stressed that if results are to be comparative a standard procedure must be employed. Duration of exposure to heat, rest versus activity, grossly abnormal diets and other factors which will be described elsewhere have important influences on the electrolyte content of sweat. It is likely that each of these factors produces a change in adrenal cortical activity.

5. In many cases of masculinizing ovarian tumors, classification of the origin of androgen-producing cells on a morphologic basis has proved to be extremely difficult. In the case described here, Dr. C. V. Weller reported the presence of "large cells with hyperchromatic nuclei, resembling the cells of adrenal cortical carcinomas" and concluded that "it seems best to classify this for the present as an adrenal cortical tumor." It is possible that future study of tumors of this type will reveal a different origin of the cells which, at present, must be called adrenal-cortex-like cells. If this should prove to be the case for the androgen-producing cells of this tumor, the absence of excessive production of desoxy-like corticosteroids, as reflected in the results of the sweat tests, would be entirely clear.

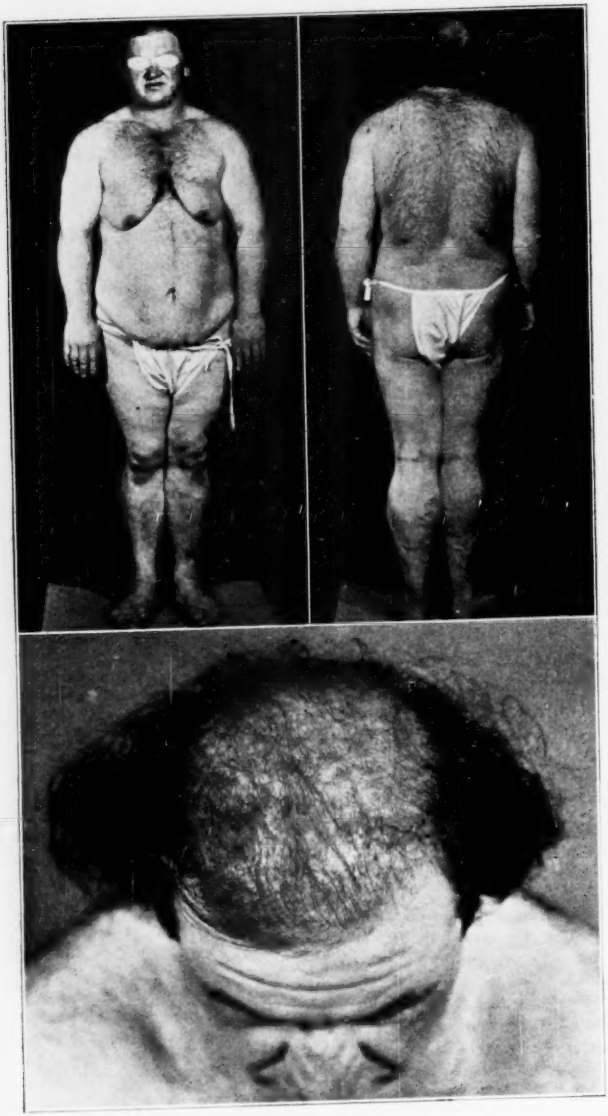

Fig. 6.—Virilization and tremendous muscular development in patient L. N.

The results shown in figure 7 require but one additional comment. The levels of sweat sodium and chloride observed in the cases of panhypopituitarism are of unusual interest. Many, but not all, patients with this syndrome exhibited no apparent disturbance of electrolyte metabolism. This is, of course, in sharp contrast to patients suffering from Addison's disease. The sweat values obtained in panhypopituitarism indicate a deficiency of desoxy-like steroids but a milder deficiency than that which exists in Addison's disease. This should not be too surprising in view of the facts (1) that most patients classified as having this condition are not completely devoid of pituitary function and (2) that functionally hypophysectomy is not equivalent to adrenalectomy. Furthermore, the amount of desoxycorticosterone required to correct completely electrolyte metabolism in Addison's disease is, in terms of milligrams, extremely small in comparison with the amounts of other pure steroids [6] needed to correct

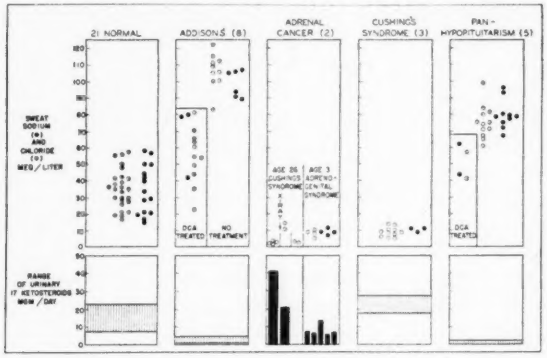

Fig. 7.—Application of sweat test in clinical disorders of adrenal cortical function.

the defect in carbohydrate metabolism found in these patients. If the estimation of Ingle and others [7] is anywhere near correct, the capacity of the normal cortex to produce steroids (again in terms of milligrams) is tremendous. It would seem reasonable, therefore that in "panhypopituitarism" any small residuum of functioning adrenal cortex could maintain electrolyte metabolism in a more normal state than

6. Forsham, P. H.; Thorn, G. W.; Bergner, G. E., and Emerson, K., Jr.: Metabolic Changes Induced by Synthetic 11-Dehydrocorticosterone Acetate, Am. J. Med. **1**:105-134 (Aug.) 1946.

7. Ingle, D. J.; Li, C. H., and Evans, H. M.: The Effect of Adrenocorticotrophic Hormone on the Urinary Excretion of Sodium Chloride, Potassium, Nitrogen and Glucose in Normal Rats, Endocrinology **39**:32-42 (July) 1946.

it could those functions which require much larger amounts of corticosteroids for their maintenance. In any case, it is a fact that much greater variability in the capacity to maintain normal electrolyte metabolism is observed in cases of "panhypopituitarism" than in cases of Addison's disease.

COMMENT

Most of the points relative to the data presented have been discussed already. However, there are several important implications, with respect both to clinical and to investigative medicine, which are inherent in the development of an index of the activity of the desoxy-like corticosteroids. It has been established in many clinical abnormalities of adrenal cortical function, as well as in physiologic states in which unusual cortical function is evident, that depression and excitation of the various functional activities do not necessarily parallel each other.[8] Thus, Venning and Browne [4] have shown that in Cushing's syndrome the predominant increase in urinary steroid excretion involves those compounds which affect protein, carbohydrate and uric acid metabolism ("11-oxysteroids") while the androgenic excretory steroids (17-ketosteroids) are mildly or not at all increased. They [9] and Forbes and others [10] have shown a similar dissociation in normal persons following severe stress, the "11-oxysteroids" excretion remaining high as the excretion of 17-ketosteroids falls below the prestress level. What is the level of activity of the desoxy-like steroids in these conditions? The tendency of patients in the first three postoperative days to retain unusually large amounts of administered sodium chloride is well recognized.

In feminizing syndromes of the male produced by adrenal cortical tumors the predominant steroid produced in excess has estrogenic properties. Yet histologic examination of such tumors gives no clue as to why the adrenogenital syndrome develops in one person, Cushing's syndrome in another and feminism in a third. Some diseases of man may be associated with the predominant production of excessive amounts of desoxy-like corticosteroids. Notable anasarca need not be an accompaniment of the excessive production of desoxy-like corticosteroids.

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8. Talbot, N. B.; Albright, F.; Saltzman, A. H.; Zygmuntowicz, A., and Wixom, R.: The Excretion of 11-Oxycorticosteroid-like Substances by Normal and Abnormal Subjects, J. Clin. Endocrinol. **7**:331-350 (May) 1947.

9. Venning, E. H.; Hoffman, M. M., and Browne, J. S. L.: The Extraction of Cortin-like Substances from Human Post-Operative Urine, Endocrinology **35**:49-62 (July) 1944.

10. Forbes, A. P.; Donaldson, E. C.; Reifenstein, E. C., and Albright, F.: The Effect of Trauma and Disease on the Urinary 17-Ketosteroid Excretion in Man, J. Clin. Endocrinol. **7**:264-288 (April) 1947.

It seems possible, then, that in some physiologic states associated with stress, as well as in some pathologic conditions, the adrenal steroids produced in excess may be mainly of the type which affects electrolyte metabolism. Selye's concept [11] of diseases of adaptation is intriguing in this regard, despite the fact that evidence is not yet available to support it. However, it has been with desoxycorticosterone that he has been able to produce in experimental animals certain vascular, myocardial and synovial lesions which he suggests may be the equivalent of those frequently observed in man. An index of the activity of the desoxy-like corticosteroids should be helpful in the further study of these and other conditions which may be related to increased adrenal cortical function.

SUMMARY

Under standard conditions of testing, the concentrations of sodium and chloride in the sweat of normal persons fall within the range of about 15 to 60 milliequivalents per liter, with a mean value of 42 milliequivalents per liter. Administration of desoxycorticosterone acetate or of purified pituitary adrenocorticotropic hormone produces a great fall in these levels and a reversal of the normal relationship of sodium to chloride. When adrenocorticotropic hormone is employed, evidence of increased production of androgenic steroids and of "11-oxysteroids" is observed, in addition to the desoxy-like corticosteroid effect. The levels of sodium and chloride in sweat appear to reflect the degree of activity of those corticosteroids which affect electrolyte metabolism (the desoxy-like corticosteroids).

Patients with untreated Addison's disease show concentrations of sodium and chloride in sweat far in excess of the highest normal values. Administration of desoxycorticosterone or of lipoadrenal cortex® brings down these increased levels. They rise again on cessation of treatment. These values are helpful, therefore, both in diagnosis and in the evaluation of therapy.

In 2 cases of proved adrenal cortical carcinoma, in 1 of which Cushing's syndrome was exhibited and in the other the adrenogenital syndrome, the concentrations of sodium and chloride in the sweat were extremely low. A woman with extreme masculinization and increased urinary 17-ketosteroids had normal concentrations of sodium and chloride in the sweat. It is evident that many syndromes may be produced by increased adrenal cortical function, each depending on the relative preponderance of one type of corticosteroid over the others.

Sweat sodium and chloride values in Cushing's syndrome, not associated with adrenal cancer, were at or below the lowest levels obtained

11. Selye, H.: The General Adaptation Syndrome and Diseases of Adaptation, J. Clin. Endocrinol. **6**:117-230 (Feb.) 1946.

in normal persons. They were considerably higher than those obtained in the 2 cases of carcinoma studied.

Panhypopituitarism gives values which fall between the upper limit of normal and the high levels observed in Addison's disease.

It is predicted that some pathologic conditions not yet linked to the adrenal cortex, as well as the physiologic response to some forms of stress, will be found to be associated with a preponderant activity of the desoxy-like corticosteroids. A simplified method is being studied for carrying out the sweat test in the clinical laboratory.

Invaluable assistance was given by the following members of the laboratory staff: Dr. Lawrence H. Louis, Dr. Margaret W. Johnston, Miss Betty Johnson, Mrs. Shirley Wark, Mrs. Betty Sprunger, Mrs. Elizabeth Pinkham and Mrs. Shirley Browne.

ABSTRACT OF DISCUSSION

DR. BENJAMIN F. SIEVE, Boston: In fairness to the audience, who are always a little bewildered by laboratory procedure, particularly endocrinologic, I think they should be made familiar with the work of Thorn and his group during the past fifteen months, which was reviewed at the meeting of the Association for the Study of Internal Secretions on Friday. They have developed a simple test, that can be done by any laboratory, which shows much promise. It involves a special technic on the blood counts of the general circulation, in which there is a definite decrease in circulating eosinophils in a proportion which has been worked out by Thorn and his group.

It is important for the audience to realize that a test as simple as this can be done to establish definitely or rule out the presence of adrenal insufficiency.

DR. J. G. G. BORST, Amsterdam, Holland: I should like to ask whether Dr. Conn has made any analysis of the sweat in patients with shock. Patients with shock usually perspire profusely. It would be interesting to know if there is a reduction in sodium and chloride figures.

DR. JEROME W. CONN, Ann Arbor, Mich.: Dr. Thorn's test for Addison's disease is a good one, but it is a test for adrenal insufficiency. The sweat sodium and chloride gives an index of increasing as well as decreasing adrenal cortical function. Thorn's test involves the injection of 25 mg. of adrenocorticotropic hormone, two counts of circulating eosinophils and determinations of uric acid and creatinine on a four hour urine specimen. In our test we need only the sweat chloride content. This is not to indicate that this test is better for the diagnosis of Addison's disease than Thorn's test. The drop in the blood eosinophils and the increase in urinary uric acid which occur in normal persons on administration of adrenocorticotropic hormone are functions of the "11-oxysteroids." They give no indication of the production of desoxy-like steroids. The main point that I want to make with respect to this data is that it is the only method that we have available today which will give us an index of the production of those steroids which affect electrolyte metabolism.

With regard to the second question, we have not studied any patients in shock.

BLOOD PRESSURE LEVELS IN THE NETHERLANDS DURING THE WAR

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DURING the years of occupation, 1940 to 1945, the weight of many inhabitants of the Netherlands decreased as noted both in the clinics [1] and among the general population.[2] At the same time, there was a fall in blood pressure to levels far below those regarded as normal. However, before one can judge whether or not these levels were actually low, it is necessary to investigate the standards that are applied in the determination of normal blood pressure.

NORMAL BLOOD PRESSURE

The literature abounds in information on normal values for blood pressure. Until twenty or thirty years ago, many authors accepted a maximum blood pressure of 150 to 160 mm. of mercury as normal, stating that the most frequently prevailing systolic range was 130 to 140 mm.[3] These reports did not tend to fix a definite limit but drew attention to the variability of a normal blood pressure and the impossibility of determining an absolute standard. Alvarez and his associates [4] and

From the Laboratory of Physiology, University of Amsterdam.

1. Sindram, I. S.: De invloed der tijdsomstandigheden op den bloeddruk der zwangeren, Nederl. tijdschr. v. geneesk. **87**:1414-1417 (Sept. 4-11) 1943.

2. Rombach, K. A.: Onze patienten in de tegenwoordige omstandigheden: Daalt de bloeddruk? Nederl. tijdschr. v. geneesk. **86**:1848 (July 18) 1942; **87**:1509 (Sept. 18-25) 1943.

3. Saller, K.: Ueber die Altersveränderungen des Blutdrucks, Ztschr. f. d. ges. exper. Med. **58**:683-709, 1928.

4. Alvarez, W. C., and Stanley, L. L.: Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards: Statistical Analysis, Arch. Int. Med. **46**:17-39 (July) 1930. Alvarez, W. C.; Wilzen, R.; Taylor, F. B., and Starkweather, E.: Blood Pressure in University Freshmen and Office Patients, ibid. **26**:381-404 (Oct.) 1920. Alvarez, W. C.; Wilzen, R., and Mahoney, L. J.: Blood Pressure in Fifteen Thousand University Freshmen, ibid. **32**:17-30 (July) 1923.

Symonds [5] fixed a maximum systolic level of 150 mm. and regarded any higher reading as pathologic. Through the pioneer work of Hunter and Frost,[6] Alvarez and Symonds, the height of normal diastolic pressure was finally fixed at 90 mm. of mercury, but even this level was found not to be static.

MEANING OF "NORMAL"

Are these fixed levels really normal for healthy persons? Normal values have been more or less established by the insurance companies and are based on their mortality statistics, but the more recent work of Robinson and Brucer [7] showed that these limits are so great that some persons with high, so-called normal, blood pressure in reality have incipient hypertension. These authors pointed out that the blood pressure level most conducive to a low death rate lies below 120 systolic and 80 diastolic. A person whose blood pressure fluctuates higher than this during a twenty-four hour day and continues to do so throughout the years will become, within a ten year period, definitely hypertensive. A level of 130 systolic and 90 diastolic will undoubtedly lead to hypertension within a few years, according to Robinson and Brucer, and one of 140 systolic and 90 diastolic they considered irrefutable hypertension at any age. These authors also stated that the range of blood pressure between 130 and 140 systolic and 85 and 90 diastolic should be considered prehypertensive, since this will definitely increase with age, even though when taken it was considered within normal limits. The average blood pressure, even though it varies, is merely a value determined by comparison of blood pressure fluctuations in normal persons. It is agreed that the level will normally increase slightly with age. Robinson and Brucer, in 1939, examined more than 10,000 patients and followed 500 of them over a ten year period to determine what the average fluctuation might be in normal persons and what the average incidence in increase of blood pressure was as compared with advancing age.

CRITERION FOR REST VALUE

Before adoption of criteria for the measurement of normal working blood pressure, it was first necessary to establish a normal rest value. We accepted as the rest value the blood pressure level reached by the relaxed test subject within a certain length of time. Some workers

5. Symonds, B.: The Blood Pressure of Healthy Men and Women, J. A. M. A. **80**:232-236 (Jan. 27) 1923.

6. Hunter and Frost, cited by Ayman, D.: Normal Blood Pressure in Essential Hypertension, J. A. M. A. **94**:1214-1218 (April 19) 1930.

7. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure: A Statistical and Clinical Study of 11,383 Persons, Arch. Int. Med. **64**:409-444 (Sept.) 1939.

considered a rest period of fifteen minutes sufficient; others required twenty minutes. Hines [8] showed that patients with hypertension must rest at least thirty minutes before normal values are reached. After the basal level is attained, blood pressure readings should vary not more than 4 mm. of mercury on repeated determinations. On the basis of experiments conducted by Wright and associates [9] and Shock and Ogden [10] to determine percentage of error in reading blood pressure values, we believe that a difference of less than 4 mm. of mercury in two successive measurements, taken between one and one and one-half minutes apart, is within the limit of error. A difference of more than 4 mm. means either that the patient has not reached his basal rest value or that he has an extremely labile blood pressure. We further believe that the real basal level of any person is that one attained after an unbroken night's sleep and before food is taken.

CRITERIA FOR BLOOD PRESSURE READINGS

In our blood pressure readings, we adopted the criteria established by the American and British committees [11] on the standardization of blood pressure readings in 1930.[11a] The first systolic pressure was determined as the first murmur heard when the blood pressure cuff was deflated, and the diastolic reading was taken at the change of sound

8. (*a*) Hines, E. A., Jr.: The Hereditary Factor in Essential Hypertension, Ann. Int. Med. **11**:593-601 (Oct.) 1937; (*b*) Range of Normal Blood Pressure and Subsequent Development of Hypertension: A follow-up Study of 1,522 Patients, J. A. M. A. **115**:271-274 (July 27) 1940; (*c*) Reaction of Blood Pressure of Four Hundred School Children to Standard Stimulus, ibid. **108**:1249-1250 (April 10) 1937; (*d*) Significance of Vascular Hyperreaction as Measured by Cold-Pressor Test, Am. Heart J. **19**:408-416 (April) 1940; (*e*) Technic of Cold Pressor Test, Proc. Staff Meet., Mayo Clin. **14**:185-187 (March 22) 1939. (*f*) Hines, E. A., Jr., and Brown, G. E.: The Cold Pressor Test for Measuring the Reactibility of Blood Pressure: Data Concerning Five Hundred and Seventy-One Normal and Hypertensive Subjects, Am. Heart J. **11**:1-9 (Jan.) 1936; (*g*) A Standard Test for Measuring the Variability of Blood Pressure: Its Significance as Index of Pre-Hypertensive State, Ann. Int. Med. **7**:209-217 (Aug.) 1933.

9. Wright, I. S.; Schneider, R. F., and Ungerleider, H. E.: Factors of Error in Blood Pressure Readings: Survey of Methods of Teaching and Interpretation, Am. Heart J. **16**:469-476 (Oct.) 1938.

10. Shock, N. W., and Ogden, E.: The Probable Error of Blood Pressure Measurements, Quart. J. Exper. Physiol. **29**:49-62 (March) 1939.

11. Standard Method for Taking and Recording Blood Pressure Readings, Committee for the Standardization of Blood Pressure Reading of the American Heart Association, J. A. M. A. **113**:294-297 (July 22) 1939; Am. Heart J. **18**:95-101 (July) 1939.

11a. Kaiser, L.: Auscultation of Blood Pressure, Nederl. tijdschr. v. geneesk. **63**:233-239 (July 26) 1919. Peters, J. T.: Systolic and Diastolic Pressure, ibid. **67**:1844-1848 (Nov. 3) 1923.

as the mercury continued to fall.[12] Many clinics still prefer to regard the point of disappearance of murmur as the diastolic level.[13] This, however, does not give a satisfactory determination in those conditions in which the murmur continues, such as aortic insufficiency. It is better to note the disappearing murmur of the blood pressure as "tone pressure"[14] rather than as diastolic murmur, so that in conditions such as aortic insufficiency the change in tone is recorded as the direct diastolic pressure, whereas the persistence of murmur down to 0 is indicated as "tone pressure." In the same way, extreme changes in the difference in auscultatory amplitude[14b] between systolic pressure and "tone pressure" may be considered indicative of a disturbance in circulation and a first manifestation of vascular reaction.

"WORK" PRESSURE AND THE COLD PRESSOR TEST

We should like to draw attention to a phenomenon peculiar to the initial determination of blood pressure. We believe that the first clinical determination of a patient's blood pressure is often too high and cannot be trusted as an impression of an average level. We called this blood pressure "work" pressure as compared with the rest value. Our work pressures often corresponded to levels obtained with the cold pressor test of Hines in the hyperreactive person. Work pressure is the level attained after running, climbing stairs or carrying heavy burdens; it may also result from psychologic factors. Following Hines and Brown to a certain extent, we classified our subjects as: (1) hyporeactive persons; (2) normal, hyperreactive persons, with blood pressure at rest below 145 systolic and 95 diastolic, with a tone pressure of 90, but with a systolic or diastolic reaction of more than 20 mm. of mercury; (3) prehypertensive persons, with blood pressure above the maximum limit (145 systolic and 95 diastolic), or who, in addition to their increased tension, showed a stronger reaction on the cold pressor test. We avoided use of the term hypertensive because, other than the cold pressor test, we made no attempt to prove hypertension.

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12. Giesen, J.: Bloedsdrukmeting, Amsterdam, Ellerman & Harms Ltd., 1934; Korotkov Sound Phenomenon: Spontaneous Development and Artificial Production of Arterial Sound in Man, Nederl. tijdschr. v. geneesk. **79**:3528-3540 (July 20) 1935.

13. Brown, G. E.: Clinical Tests of Function of Autonomic Nervous System, J. A. M. A. **106**:353-357 (Feb. 1) 1936.

14. (*a*) Aalsmeer, W. C.: Een critische beschouwing der Amerikaansch-Britische voorstellen tot standaardisatie van de bepaling van den diastolischen bloeddruk, Nederl. tijdschr. v. geneesk. **87**:435-437 (March 6) 1943. (*b*) Brandsma, K., and Nieuwmeijer, A. H.: Is de bloeddruk in oorlogstijd verlaagtd? ibid. (supp.) **5**:41-45, 1944.

As previously observed by Brada and Feil,[15] we found that the blood pressure after the cold pressor test often fell below rest value, but such an observation is reliable only when the rest value has been established. If, however, the rest value has been determined and it falls within the reading error of 4 mm. of mercury, the fall in blood pressure immediately after a cold pressor test is regarded as corporeal overcompensation which is apparently due to abnormally prolonged vascular relaxation caused by persistent and severe constrictive phenomena.

PULSE

In other studies as a rule, results of the cold pressor test were correlated only with age; other elements such as pulse rate, length and weight of the body were not taken into account. White and Gildea[16] correlated the pulse and blood pressure and reported that a rapid pulse is associated with an anxiety state. Rautmann[17] classified pulse rates as very low to very high (49 to 105) and was of the opinion that a normal pulse at rest should be between 65 to 78, the optimum being about 71.2. Other investigators stated that normal values should be much higher. In a group of men who averaged 24 years of age, Franke[18] observed the average normal rate to be 78.1, varying from 68 to 88 beats per minute. Wunderlich[19] reported the average resting pulse of 77.4, with a range of 48 to 116 pulsations. Franke restricted his studies to those patients having systolic blood pressures of 115 to 145 mm. of mercury without consideration of the relation between blood pressure level and pulse rate.

In performing work, the blood pressure rises and the pulse rate increases. This fact applies to a lesser degree to trained persons than to those who are untrained. Rautmann observed that the average raise in pulse rate for a trained person after genuflecting was

15. Brada, H., and Feil, L.: Die Blutdruckreaktion auf Kältereiz, Wein. Arch. f. inn. Med. **31**:121-128, 1937.

16. White, B. V., Jr., and Gildea, E. F.: "Cold Pressor Tests" in Tension and Anxiety: A Cardiochronographic Study, Arch. Neurol. & Psychiat. **38**:964-984 (Nov.) 1937.

17. Rautmann, H.: Ueber die Gewinnung von Bestimmungstabellen mit Hilfe des Korrelationsverfahren, Ztschr. f. d. ges. Anat. (Abt. 2) **13**:477-486 (Jan. 16) 1928; Untersuchungen über die Norm, Jena, Gustave Fischer, 1921.

18. Franke, K.: Ueber die Variabilität der Puls- und Atemzahl bei kreislaufgesunden, körperlich gut entwickelten jungen Männern, Ztschr. f. d. ges. Anat. (Abt. 2) **13**:575-587 (Jan. 16) 1928.

19. Wunderlich, H.: Blutdruck und Puls bei körperlich gut entwickelten deutschen Studenten und ihre Beziehungen zu verschiedenen Körpermassen, Ztschr. f. Konstitutionslehre **18**:349-358, 1934.

12.6 per minute. Franke noticed a rise of 29.1 beats per minute in untrained persons on the average, but the pulse rate could become as high as 144 beats per minute.

For the present series of subjects, whose ages varied from 15 to 60 years, a standard exercise had to be adopted which could be performed equally well by the younger and the older persons. We chose an exercise of the abdominal muscles, in which the test subjects executed 10 quick movements from the lying to the sitting position. We observed that the results compared favorably with those obtained after 10 deep genuflections.

After performance of our standard test, the normal pulse rate fell to its rest value within one minute. This period was noted as "restitution time"; however, it was advisable to check the pulse for longer than one minute because rate fluctuations around the normal values occurred.

A positive relation existed between the restitution time and the time of activity which could be correlated, in term, with the resting pulse rate. The restitution time was more affected by training than the pulse acceleration rate during the first ten seconds of exercises. The pulse rate in a well trained subject within one minute often dropped to below normal levels, whereas the rate of an untrained person was higher over a longer period. In a person with hypertension, the pulse acceleration rate was higher than normal, even though the resting pulse rate was within normal limits. White and Gildea observed that after the cold pressor test an increase in pulse rate up to 102 per minute occurred in hypertensive persons, while the normal person reacted by a rise to only 75 to 79 beats per minute.

LENGTH AND WEIGHT OF THE BODY

There is said to be a correlation between length and weight and blood pressure. The percentage of tall men having high blood pressure is greater than that of short men. Faber (1924),[20] on examining 1,000 healthy soldiers, confirmed previous reports that among men having the same height the blood pressure rose with the weight. Huber,[21] Symonds,[5] Burlage,[22] Faber [20] and van Mervennee and Smed-

20. Faber, H. K.: A Formula Expressing a General Relationship Between Blood Pressure and Body Weight, Proc. Soc. Exper. Biol. & Med. **25**:77-80 (Nov. 27) 1927.

21. Huber, E. C.: Systolic and Diastolic Blood Pressure in Healthy Men, Human Biol. **5**:541-576 (Dec.) 1933; Systolic Blood Pressure of Healthy Adults in Relation to Body Weight, J. A. M. A. **88**:1554-1557 (May 14) 1927.

22. Burlage, cited by van Mervennee and Smeding.[23b]

ing [23] advocated that height and weight, as well as age, must be considered if the blood pressure level is to be correctly judged. Sindram [1] was of the opinion that the decrease in blood pressure among pregnant Dutch women during the war was due to food deficiencies. The weight of the men also fell, but in a great many persons the blood pressure was unchanged or higher than previously, probably because of psychologic factors.

MATERIAL AND METHOD

To investigate the various problems reviewed in the preceding paragraphs, and to determine whether or not during the war blood pressure in the Netherlands tended to drop to lower values, we made a study of 250 men whose ages varied from 15 to 60 years and who performed light to heavy work in an Amsterdam factory. Light labor was considered office work, and heavy labor involved lifting heavy burdens. We also noted the kind of labor performed by each subject in the factory, distinguishing such activities as standing, walking and sitting. Men were considered healthy who had no subjective or objectively perceptible complaints. Care was taken to rule out all persons with cardiovascular disease, genitourinary disease, diabetes or contagious illnesses. No one was accepted for study who was addicted to alcohol or heavy use of tobacco or to sedatives or narcotics. Family histories of cardiovascular disease were not considered.

The men were told of the experiment, which was to take place in the surroundings to which they were accustomed so that they were not disturbed by the tests. Many thought it interesting and gave their whole-hearted cooperation. The tests were performed from October 1943 to March 1944, between 2:30 and 5 p. m. They were done in such a way that the same investigator always made the same determination on the same person in order to reduce the percentage of error. During the initial period, after a short anamnesis, the height and the weight of the test subjects were noted. Blood pressures were determined on all persons in a sitting position. Three successive blood pressure values were determined by auscultation in conformity with the previously noted criteria. First, the entering or "work" blood pressure was obtained, values for which may be compared with an initial determination made in a clinic. Second, the level on exercise was determined within ten seconds after the patient had risen from a recumbent to a sitting position ten successive times. Third, the blood pressure was taken after an average of twenty-three minutes of rest. Fourth, the level on reaction to the cold pressor test, in which the right hand was dipped in ice water at 4 C., was read at thirty to sixty seconds. The pulse rate was recorded with each pressure determination.

RESULTS

To reduce chances of error in recording the blood pressure values to a minimum, averages of duplicate determinations were accepted when the difference was less than 10 mm. of mercury. The blood pressure after activity involved one measurement taken immediately following exercise. During the cold pressor test the gross rise in

23. van Mervennee, C. J., and Smeding, T.: (*a*) Bloeddruk en sportkeuring, Nederl. tijdschr. v. Soc. geneesk., 1939, pp. 61-66; (*b*) Medische sportkeuring, Amsterdam, Kosmos, 1939.

blood pressure within one and one-half minute was recorded. It is well known that blood pressure is not static in a normal person, and an attempt was made to survey the fluctuations as completely as possible or practical. One of the most obvious correlations is that between blood pressure and the variable age. Consequently, it has

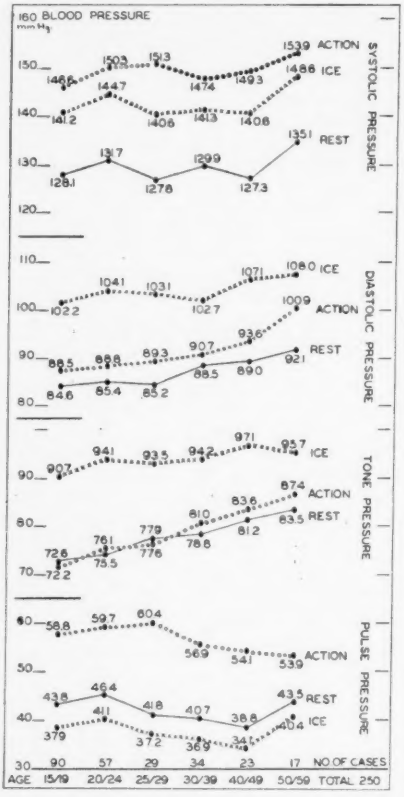

Chart 1.—Average systolic pressure, diastolic pressure, tone pressure and pulse pressure as determined for a group of 250 normal Dutch men. Men over 30 years old were placed in ten year age groups.

been studied more than the correlation of blood pressure with pulse rate, height or weight. In this study comparisons were made on several bases with results obtained by other investigators.

In the determination of the rest blood pressure, the tension was measured after an average of twenty-three minutes in the supine

position, with a variation, depending on the entrance value, of fourteen to forty-five minutes. Those subjects with arterial tensions higher than 145 systolic and 95 diastolic were required to rest at least thirty minutes. It was felt that a prolonged rest period would nullify the manual daily fluctuations in the blood pressure; therefore, a rest period of more than forty-five minutes was not allowed. No attempt was made to find the basal value by this test.

TABLE 1.—*Average "Rest" Blood Pressure with Standard Deviation and Variations in Range and Blood Pressure of 250 Normal Men*

	Relation of Age to "Rest" Blood Pressure in 250 Men (Total Group)						
							All Ages
Age group	15 to 19	20 to 24	25 to 29	30 to 39	40 to 49	50 to 59	15 to 59
Number of readings	180	114	58	68	46	34	500
Percentage of total	36	22.8	11.6	13.6	9.2	6.8	100
Systolic Pressure, Mm.							
Mean	128.1	131.7	127.8	129.9	127.3	135.1	129.5
Standard deviation (±)	13.8	14.2	9.7	11.8	12.8	17.3	13.6
Probable error (±)	1.03	1.33	1.28	1.43	1.89	2.9	1.93
Variation range	95 to 160	104 to 169	107 to 141	111 to 163	96 to 155	109 to 166	95 to 160
Central	127.6	130.4	127.9	129.2	127.9	136.7	128.6
Modal	125.9	140.7	126.9	130.0	135.2	134.6	126.7
Percentage							
>145 and <150	15.6	8.0	0	0	0	19.6	8.8
>145	22.2	19.3	0	11.8	4.4	38.2	17.0
>130	41.7	51.0	41.4	47.1	41.4	55.9	45.4
<120	24.4	17.6	17.2	17.6	17.4	17.7	20.4
<110	7.2	6.1	3.4	0	13.1	8.8	6.2
Diastolic Pressure, Mm.							
Mean	84.6	85.4	86.2	85.5	89.0	92.1	86.3
Standard deviation (±)	9.4	10.7	7.6	10.2	9.02	13.1	8.3
Probable error (±)	2.23	1.0	1.0	1.23	1.33	2.19	1.37
Variation range	59 to 108	63 to 113	68 to 106	72 to 129	67 to 107	74 to 119	59 to 129
Central	85.3	86.7	85.4	87.5	90.0	91.0	86.6
Modal	83.6	84.4	85.2	82.6	90.9	90.0	86.5
Percentage							
>100	3.9	6.1	3.4	10.3	10.9	23.5	7.2
> 95	12.2	36.0	8.7	20.6	13.1	47.0	20.8
< 80	28.9	27.2	19.0	14.7	13.1	17.6	23.2
< 70	5.0	6.8	1.7	0	2.2	0	4.2

Average Rest Blood Pressure.—The average blood pressure at rest for our series, considering all age groups, was 129 systolic and 86 diastolic, with a tone pressure of 76.2. These figures correspond with those of Alvarez,[4] Saller[8] and Robinson and Brucer.[7] The range of standard deviation, from plus to minus 13, depending on the age studied, the larger value being for the older age group, is not unusual in view of the small number of persons (17) in the older group (50 to 60 years). The standard deviation for diastolic pressure was plus or minus 8.3.

Limited Mean Pressure.—In the series examined, two thirds of the patients had blood pressures below 145 systolic and 95 diastolic. This was considered an average level which at the same time suited criteria for the so-called normal. This is a little above the optimum

normal of 140 systolic and 90 diastolic as established by Robinson and Brucer, and below the normal of 150 systolic and 95 diastolic established by Hunter and Frost [6] and Symonds.[5]

The average age of the men examined was 27.3 years plus or minus 11.4. Sixty-eight per cent of all subjects were in the age group of 15 to 38 years, which established the mean level at about 27 years of age.

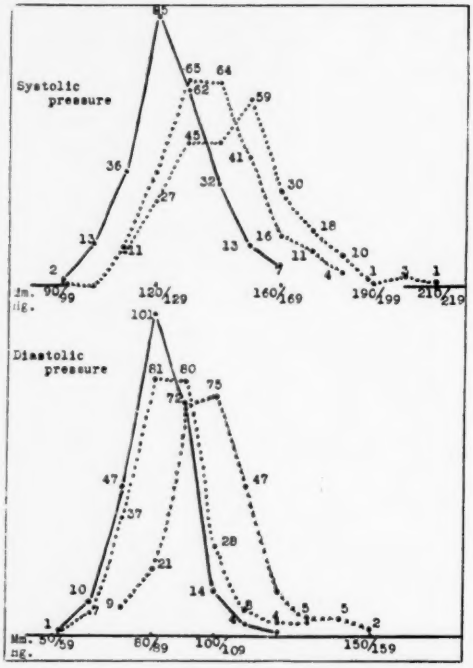

Chart 2.—Curves showing deviations in the systolic and the diastolic pressures in 250 normal Dutch men. Figures show number of men with indicated pressures.

When persons with signs of prehypertension were eliminated, the average blood pressure corrected for this group was 126 systolic and 83 diastolic. The modal value also sustained slight modification; it was 129.1 systolic and 84.4 diastolic. Robinson and Brucer with their limited group reported a systolic value below 120 mm. for half their series and below 130 mm. for three-fourths. It is remarkable that we found only 24.3 per cent with systolic pressure of less than

120 mm. and only 37.8 per cent between 130 and 145, especially when 43.5 per cent of the series was between 20 and 24 years of age and 41.4 per cent between 25 and 29. The curve for the limited group shows that prehypertensive persons were dropped out all along the line.

The curve for reduction in diastolic pressure was similar, though not so marked, because the general course of diastolic pressure is more uniform and rises with age. In contrast to the results of Robinson and Brucer, who recorded 79.8 per cent below 80 mm., our figures showed 23.3 per cent below that figure, and 7.2 per cent with diastolic pressure of 100 mm., which though not of pathologic implication was certainly abnormal. The blood pressure values below 70 mm. occurred chiefly in the youngest group, i.e., in persons 14 to 19 years of age.

The systolic pressure in persons between 18 and 24 years was high; the average was 131.6 mm. of mercury and it was 127.2 among the limited group of younger persons. The difference in diastolic pressure was negligible. Hence it was necessary to consider only the systolic pressure in a study of possible subjective or objective manifestations of psychologic tensions.

"Work" Blood Pressure.—The first blood pressure determination taken immediately after the subject presented himself was often quite high and might have been influenced by physiologic conditions or emotional reactions. It was rightly considered a "work" blood pressure. The average systolic level was 4.2 mm. of mercury above the rest value. This difference from the rest blood pressure was approximately the same for persons of all ages. The diastolic pressure of excited persons showed an average difference between values for work and rest of 1.5 mm. We have, therefore, drawn the same conclusion as Addis [24] and Braun and Schellong,[25] namely, that the diastolic pressure rose little and even decreased at times.

Blood Pressure After Exercise.—The reaction after exercise as the expression of increased activity of the heart is especially notable in the systolic pressure. The test subjects examined in this respect showed an average increase of 19.5 mm. in systolic pressure. Training proved to have little influence on older or younger persons, though, as might have been expected, younger persons performed the exercise with less exertion. The group 40 to 49 years of age exceeded the general average increase in systolic pressure, showing a 22.0 mm. increase, but the 25 to 30 year group was higher, with an average reac-

24. Addis, T.: Blood Pressure and Pulse Rate Levels: I. The Levels Under Basal and Daytime Conditions, Arch. Int. Med. **29**:539-553 (April) 1922.

25. Braun, E., and Schellong, F.: Ueber die konstitutionellen Grundlagen der essentiellen Hypertonie, Deutsche med. Wchnschr. **62**:371-373 (March 6) 1936.

tion of 23.5 mm. Comparison of these groups with the others tested shows that the reaction from muscular exercise was strong. A special reason for this cannot be advanced; neither the work blood pressure of these groups nor their levels on the cold pressor test showed such a reaction. Frequently, totally unmeasurable factors were accountable, such as concentration, exertion and subjective adjustment to the muscular exercise.

According to Mateeff and Petroff (1931),[26] the diastolic pressure may react variously to muscular work; it may increase, decrease or remain the same. Increase or decrease of tension was regarded by these authors as a consequence of decreased adaptability to modified static or dynamic conditions. These reactions occur oftener in older persons, as with age both endurance and adaptability decrease. The diastolic curve also shows a considerable increase in the group between 50 and 59 years of age.

Extensive data have been collected with respect to pulse rate after muscular labor and its restitution time, but little attention has been given the relation between blood pressure on exercise and the time required for a return to the initial value. For such an investigation we recommend continuous registration by an oscillator.

However, in this report we prefer to discuss the differences, if any, in the time required for the return of blood pressure to the initial point after exercise and after the reaction to the cold pressor test. Curiously, in 26 per cent of our total series the systolic pressure after the cold pressor test decreased until below the rest value; half of the subjects reached this value after one minute, and the other half after two minutes. The criteria for the rest value were complied with and the blood pressure changes were not within the reading error of 4 mm. Therefore, the actual differences must have been due to abnormal vascular reaction, and especially to increased peripheral dilatation. In order to judge whether there exists a generally characteristic vasolability at levels after activity and the cold pressor reactions, other combinations with rest blood pressure as the initial value must be taken into consideration.

Cold Pressor Test.—For the reaction to the cold pressor test in most cases the diastolic pressure was determined when the sound disappeared. To make our data comparable with that of other workers, it was necessary to take the difference between the systolic and the clinical diastolic pressure (tone pressure) as the reactive result of the test. We assumed a diastolic reaction to ice water of 20 mm. as the

26. Mateeff, D., and Petroff, C.: Ueber das Verhalten des diastolischen Blutdruckes nach Körperarbeit und seine Bedeutung, Klin. Wchnschr. **101**:1027-1030 (May 30) 1931.

limit for normal hyperreactive persons. The systolic difference in reaction was also fixed at 20 mm. in conformity with the values accepted by Hines in 1940. He established the average hyporeactive test value at 12 mm. systolic and 10 diastolic and the hyperreactive averages at 31 and 27 mm., respectively. It is desirable to increase the diastolic limit 5 mm. over Hines's value, as the blood pressure of a test subject on changing from horizontal to vertical position shows that increase.

The restitution time from the ice reaction was one and one-half minute for 86.2 per cent of the series, whereas only 11.6 per cent of the blood pressure levels on exercise returned to rest value within that period. Hines, with 1,842 test subjects, recorded that 92 per cent returned from cold pressor level to a rest value within that time. Thus, our figures are normal, though slightly low.

Hines (1940) [8b] calculated as average results for systolic and clinically diastolic pressure 16.0 and 13.2 mm., respectively. These figures included both hyporeactive and hyperreactive persons. The hypertensive persons reacted strongly, with averages of 46.6 mm. systolic and 30.9 diastolic.

In the study by Hines, the test subjects within the normal range comprised 85 per cent hyporeactive and 15 per cent hyperreactive persons. We found 52.8 per cent and 39.2 per cent, respectively. Our reaction values for the normal group (including hyporeactive and hyperreactive persons) were 12.8 mm. systolic and 17.4 diastolic. The systolic variations in this group were from 9.4 mm. for hyporeactive subjects to 19.1 mm. for the hyperreactive ones. The diastolic difference was 11.5 and 25.9 mm., respectively. The diastolic reaction proved to be considerably higher than the systolic one, contrary to the values reported by Hines.

In the small prehypertensive group the systolic reaction too was within the limit of 20 mm. accepted for normal subjects, namely, 11.3 mm. However, the diastolic results diverged from 5 to 63.5 mm., differences which were much larger than the systolic ones. The reason for this stronger reaction might be that these patients were sitting during their examination. With a similar procedure, van Dorp [27] with normal convalescent patients in Holland also obtained a result that was larger diastolically than systolically, ascribing this partly to their being confined to bed. Ayman and Goldshine (1938) [28] and White and Gildea,[16] utilizing patients in a sitting position and of all types from normal hyporeactive to hypertensive, reported the systolic reaction value

27. van Dorp, W. J.: Bloeddruk bij roodvonk: Met toepassing van de C. P. T., Ymuiden, 1942.

28. Ayman, D., and Goldshine, A. D.: Cold as a Standard Stimulus of Blood Pressure: Study of Normal and Hypertensive Subjects, New England J. Med. **219**:650-655 (Oct. 27) 1938.

to the ice test always larger than the diastolic. The results corresponded to those of Hines, notwithstanding the sitting position. This does not seem very significant, because only the influence of the emotional stimulus on blood pressure is verified. The differences in results were not entirely due to the various positions taken by the patients when examined. In order to judge the test correctly, it is necessary to take into consideration the systolic value as well as the diastolic, especially since Hines and Brown in 1933 [8E] characterized the systolic range as the most important criterion.

In 53.2 per cent of our series a simultaneous maximum reaction was observed. Fifty-eight per cent of the whole group remained below the systolic blood pressure level of 145 mm., whereas the maximum reaction value of 42.8 per cent was below 90 mm. Of the hyperreactive subjects 53 per cent had a ceiling value of more than 145 mm. and 75.5 per cent showed an increase in blood pressure above 90 mm. The prehypertensive subjects already showed higher values. We saw no correlation in the height of the blood pressure between the reaction and the initial value. Only in the prehypertensive group was the ice reaction and the rest value higher than among normal people.

Often a parallel can be drawn between an initial clinical measurement and the level on the ice reaction. Especially in the hyperreactive subjects did the first determination of blood pressure prove to be on the high side. Of the 98 normal hyperreactive persons, half coupled a high ice reaction (varying from 20.5 to 45.5 mm.) with a rest tension above 120 systolic and 80 diastolic. Of the 18 prehypertensive persons, only 4 had an exceedingly increased ice reaction, varying from 26 to 63.5 mm. Of the total number of normal and prehypertensive persons, 21.3 per cent had a high ice reaction and a rest value above 120 systolic and 80 mm. diastolic. However, the average blood pressure level for these persons was about 130 systolic and 85 diastolic, and this level must be accepted as normal for this group. It would be more correct to determine the percentage of those whose work tension was higher than 130 systolic and 85 mm. diastolic. The average would then be taken as the criterion for rest, whereas the percentage concerns the work tension, which on an average is already 4.2 mm. above the rest value, and undoubtedly blood pressure rises up to the height of 130 systolic and 85 mm. diastolic. It appears that 12.5 per cent of the total number comply with the relation: high work tension (i.e., more than 130 systolic and 85 diastolic) and high value on ice reaction (i. e., more than 20 mm.).

It is notable that one and one-half times as many persons have a systolic blood pressure above 130 mm. as have a diastolic blood pres-

sure above 90 mm. The diastolic difference in blood pressure between work and rest levels of 1.5 mm. may be disregarded in prehypertensive persons as well as in others.

The average rest blood pressure being approximately 130 systolic and 85 diastolic, it is not surprising that values for 44 per cent of the total number of subjects were above the limit fixed by Robinson and Brucer,[7] and that 30.8 per cent were above the limit of work blood pressure fixed by us, though their level in the ice reaction was a normal one. This blood pressure is the level on which the test subject performs his labor and it is governed by his exertions. We discovered no distinct relation between the initial (or work) blood pressure and the magnitude of the ice reaction. Nevertheless, an increased level on ice reaction must be regarded as a primary indication of prehypertension or potential hypertension.

Unlike many American writers (Hines and Brown,[8f, g] White and Gildea,[16] Ayman and Goldshine [28]), who reported a decrease in pressure to slightly above the initial value, we found a decrease in systolic blood pressure to a point below the rest value in about one fourth of all cases, the rest value being attained soon after that. Brada and Feil,[15] working in the Vienna Polyclinic (1937), observed the same phenomenon. To Hines, too, a similar decrease was known, but he doubted the correctness of the examination. However, with the taking of proper precautions, those blood pressures can be characterized as actual decreases. This so-called overshooting would then have to be imputed to an overcompensation of the body, a labile vasomotor innervation which was also pointed out by van Loon (1945).[29]

On the other hand, the diastolic pressure came back to its initial value almost always within two minutes. This emphasizes the maintenance of the constant minimum vascular tone so that the lability found its expression in the systolic pressure, in the delayed reaction to the demand for blood supply in the periphery and in the pulse rate.

A phenomenon further pointing to hyperactivity could not be found, although more than one half of this number (one eighth of the total persons tested) showed a higher pulse rate after two minutes out of ice than in ice. However, this reaction was shown not to be so rare because 14.8 per cent of the total had a greater pulse rate out of the ice than in the ice. Meanwhile of those who, besides a fall in systolic blood pressure below the limit of the rest value, showed a striking variation in pulse rate, more than two thirds had a diastolic rest value which was slightly higher than the corresponding blood pressure on

29. van Loon, J. A.: The Cold Pressor Test: Een functieproef van het vegetatieve zenuwstelsel, Utrecht, Oosthoek, 1945.

entrance. Van Loon (1945) recently pointed out that with nervous persons this diastolic pressure was often higher than the initial measurement, thus pointing toward vasolability on nervous grounds.

Pulse Pressure.—The oscillations of systolic and diastolic pressure in their mutual relations at the different group levels are clearly shown in the pulse pressure and the amplitude of auscultatory pressure (tone pressure). As the prevailing rest value for pulse pressure Kilgore [30] reported 50 mm., with fluctuations of 20 to 90 mm. in the various groups. In 1923, Norris and his associates,[31] who recorded values of 30 to 40 mm. of mercury within normal limits, regarded values downward of 20 and upward of 60 mm. as pathologic signs. The average in this investigation was 40.7 mm., with a width of variation of 16 to 104 mm. However, two thirds of all observations were within the limits of 25.2 mm. and 55.6 mm.

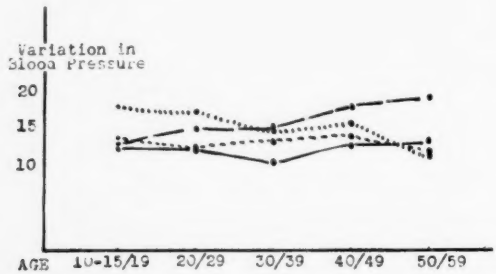

Chart. 3—Comparison of diastolic and systolic reactions (vasomotor reactivity) to the cold pressor text according to age in years. The unbroken line indicates the systolic reactions of the present series of 250 Dutch men in 1943 and 1944 and the line in long dashes the reactions recorded by Hines and Brown in their study between 1935 and 1939. The line with short dashes shows the diastolic reactions in the present series, and the vertically broken line the results of Hines and Brown.

With muscular labor the systolic pressure increases more notably than the diastolic pressure, which often even decreases or remains equal to the rest value. On prolonged exertion Addis (1922) [24] reported for systolic, diastolic and pulse pressures differences of +68, —23 and +90 mm. of mercury, respectively, from the corresponding blood pressures at rest. These are exceedingly high results. Our results for these pressure differences after the standard action test were +19.5, +3.9 and +17.9, respectively.

30. Kilgore, E. S.: Blood Pressure Measurements: Uses and Limitations in Modern Medicine, Lancet **2**:236-239 (Aug. 24) 1918.

31. Norris, G. W.; Bazett, H. C., and McMillan, T. M.: Blood Pressure: Its Clinical Applications, ed. 4, Philadelphia, Lea & Febiger, 1927.

The influence of affective tension also was ascertained by Knauer (1915) [32] on students during their examinations. In 47 per cent he observed an increased pulse pressure of 13 mm. and in 35 per cent a decrease of 16 mm. on an average. In the remaining students the pulse pressure did not change.

A cold pressor test supplies an emotional factor in addition to a direct influence on the peripheral vessels. For the present series the pulse pressure had, all along the line, a value which was less than

TABLE 2.—*Vasomotor Reactivity as Measured by the Cold Pressor Test*

	Present Series *			Series of Hines and Brown †		
		Reaction, Mm.			Reaction, Mm.	
	Per Cent of Total	Systolic	Diastolic	Per Cent of Total	Systolic	Diastolic
Normal hyporeactors.....	52.8	9.4	11.5	85	12.4	10.1
Normal hyperreactors.....	39.2	19.1	25.9	15	31.2	27.5
Normal mean.....	....	12.8	17.4	..	16.2	13.2

* The present series comprised 250 normal Dutch men whose blood pressure levels were determined in 1943 and 1944.

† This series included 1,842 persons whose levels were determined in a study conducted from 1935 to 1939.[8f]

TABLE 3.—*Vasomotor Reactivity as Measured by the Cold Pressor Test: A Comparison of the Present Series with That of Hines and Brown* [8f]

Present Series * Reaction, Mm.			Series of Hines and Brown † Reaction, Mm.	
Systolic	Diastolic	Age, Yr.	Systolic	Diastolic
		10 to 19	13.8	14.2
13.1	18.1	15 to 19		
12.6	17.7	20 to 29	15.3	13.1
11.4	15.4	30 to 39	15.5	13.8
13.3	15.9	40 to 49	18.1	14.1
13.5	12.2	50 to 59	19.7	12.5

* The present series comprised 250 normal Dutch men whose blood pressure levels were determined in 1943 and 1944.

† This series included 1,842 persons whose levels were determined in a study conducted from 1935 to 1939.

3.1 mm. below the pulse pressure at rest. The difference between the systolic and the clinical diastolic pressure applied for the cold stimulation test shows, in a few places, values even above the corresponding rest blood pressure, but for the remainder it is on the average 5.0 mm. below the rest pulse pressure. From this, it may be concluded that at the ice reaction the diastolic pressure increases more than the systolic, which is also shown by the difference between the average values for the cold stimulation test and the rest pressure, being 17.4 and 13.8 mm., respectively. It is true that the difference in pulse pressure between the reaction to the cold pressor test and rest is much smaller, namely, 5.0 mm.; nevertheless, it is noteworthy.

32. Knauer, A.: Ueber den Einfluss normalen Seelenvorgänge auf den arteriellen Blutdruck, Ztschr. f. d. ges. Neurol u. Psychiat. **30**:319-353, 1916.

Pulse Rate.—To obtain a correct insight into the blood pressure level of a delimited group of persons, a correlation with age alone is not sufficient as this reveals nothing about the physique and the conditions which are connected most closely with blood pressure. A study of pulse rate and body weight and length is certainly in its place and serves to frame the blood pressure level within the bounds which determine a standard.

In the literature, about 73 beats per minute are mentioned as an average normal rate at rest. This average is close to the value of 72.2 pulsations per minute which we determined for a test subject in a quiet sitting position. The width of variation in our series was 48 to 106 pulsations per minute, with 63.5 to 81.9 beats per minute as the most prevailing rates. That this is a rest value is proved by the fact that on entrance the pulse rate was 2 beats higher. This is not a significant difference, but it proves that during work in the factory and during the initial blood pressure measurement the pulse does not show as great a change as the blood pressure. With a cold test the pulse should not even rise appreciably, nor should the volume of pulsation change, since the cold stimulus affects only the periphery and not the heart.

In our series, then, the pulse rate in ice differed little from that at rest. Similarly, prehypertensive persons had no higher rate than the others. However, it appears that 14.8 per cent of the total series, after two minutes out of ice, had a pulse rate which, on an average, was 4.4 pulsations per minute higher than in ice. This difference, it it true, had some significance, but it had no influence on the result for the whole series. The persons from 15 to 19 years of age, a group in which juvenile hypertension is not rare, showed this special cardiac reaction and its members recovered their initial value for rest pulse after a longer than normal time.

Exertion or exercises led to increased heart activity, which was reflected in an increase in pulse rate and blood pressure. During the activity test the pulse increased 26.3 pulsations per minute on the average and values between 72 and 132 per minute were recorded. In only 7 cases was no acceleration in pulse observed in exercise. As a rule, the rest pulse was attained again within one minute; in our series thirty-three seconds was the average. Nearly 7 per cent of the total became normal within ten seconds, which might indicate a certain amount of training, although this factor could not be clearly detected.

Length and Weight.—Quantities such as length and weight were not measured for use as absolute values but only in order to ascertain whether they influence blood pressure and how far such correlation is

shown. At the turn of the century, the average body length for conscripts in the Netherlands was 164.3 cm., whereas nowadays the average is 170 cm. The most prevailing values are approximately 155 to 187 cm. In our series the average length was 171.3 cm.

The weight, which averaged 62.7 Kg., fluctuated between 79.1 and 46.3 Kg. The general experience of Symonds, that heavier persons on an average have a systolic blood pressure 10 mm. higher than lighter ones, could be confirmed in this series. The average blood pressure at a weight upward of 80 Kg. was 141.5 mm., whereas in the lightest group, weighing less than 50 Kg., it was 124.8 mm. Consequently, there was a difference of 16.7 mm. in adults 20 to 25 years of age.

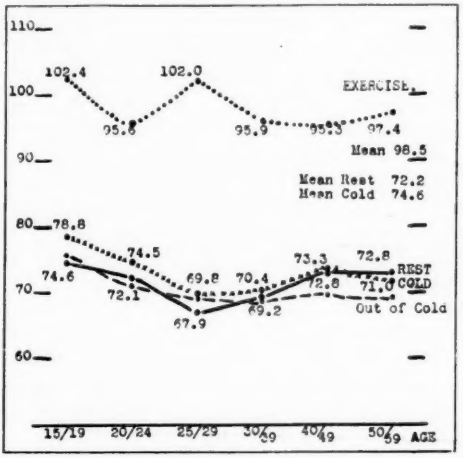

Chart 4.—Pulse rate in 250 normal Dutch men according to age, at rest, following exercise and after the cold pressor test.

The question arose whether the number of hyperreactive persons in the heavier group is larger than in the lighter group. The result was disappointing; the percentages for both groups were about equal. In the heavier group there were 14 per cent hyperreactive subjects as against 8 per cent hyporeactive and in the lighter group 17 and 6 per cent of the total, respectively. The length of the heavier group fluctuated around 180 cm. and that of the lighter group around 160 cm. Though the average weight was at the lowest limit of normal, we cannot yet ascribe it to underfeeding, notwithstanding the fact that the examination was performed in the fourth year of occupation.

COMMENT

Normal blood pressure is that value suitable to common living conditions. It is conducive to a low mortality rate and, socially and medically speaking, affords the most efficient work power, no particular deviation being found either objectively or subjectively. The establishment of a range to serve as a normal blood pressure level is, in view of the fluctuating nature of blood pressure, more satisfactory than an attempt to determine a specific static average.

As increases in the diastolic pressure characterize the conditions of beginning hypertension, the diastolic pressure with its reaction is considered a primary basis for judging a blood pressure value. With Hines we accept a critical height of 85 mm. for diastolic pressure at rest, and the tone pressure may coincide with that value.

Upward of this blood pressure the possibility of a prehypertensive condition will be greater, especially when the reaction to ice is also above the determined limit of 20 mm. of mercury. Hypertension will be almost certain when, besides the hyperreactivity, the minimum diastolic pressure shows an increase beyond 95 mm. A diastolic pressure above 100 mm. is undoubtedly a pathologic indication.

The maximum systolic criterion which we accepted was higher than that of American writers. This was due to the evaluation of the averages obtained in the present research and the standards established thereby. In our opinion a systolic pressure of 130 mm. of mercury at rest still represents a normal value, provided the initial measurement is also below this value and the cold stimulus is hyporeactive. In such a case it is fairly certain that hypertension is not present. However, we realize that our own statistical material, although including many age groups, is not conclusive. We accepted this standard only because of the conclusions of Hines and Brown and Robinson and Brucer.

Hitherto, a hypertensive level has meant a doubtful prognosis. Only a combination of values determined during rest, work, activity and exposure to cold affords a better basis for judgment of the blood pressure level. If the systolic pressure rises above 145 mm. and if there exists hyperreactivity to the cold stimulus, then, with consideration of the diastolic results, hypertension is to be expected.

The percentage of hyperreactive persons whose blood pressure is above 130 systolic and 85 diastolic (consequently being in a potential hypertensive condition) will be larger than the percentage of hyperreactive persons whose blood pressure is at or below that level (120 to 130 mm.).

With these criteria in mind, it may be ascertained whether these averages for the various age groups may be called normal and in which categories the persons in question should be classified.

The averages of 127.6 to 131.4 mm. systolic (including a probable deviation) and 85.9 to 86.7 mm. diastolic, the values for this group of workmen, are somewhat on the high side, considering the results of Robinson and Brucer. Clearly, they comprise prehypertensive blood pressure levels (145 systolic and 90 or more diastolic), if we consider that the average systolic value for the group selected fluctuated between 125.5 and 126.5 and that the average diastolic pressure was 83 mm., just under the critical point (85 mm.). The eliminated prehypertensive group proved to have a real influence on the average. Yet those blood pressures did not decrease considerably, since 37.8 per cent still had a systolic pressure larger than 130 mm. in the corrected group.

On the other hand, in this group more than half had a diastolic pressure below 85 mm., which considerably improves the estimate of hypertensiveness. If, to complete the picture, the work tension and the reaction to the cold test are included, the former does not change, whereas with the cold test the number of hyperreactive persons is conspicuous; 75.5 per cent of whom have a ceiling value above 95 mm. Without doubt, the percentage among the persons who after ten years will have hypertension will be large, corresponding to those who now have blood pressure above 130 systolic and 85 diastolic and who show hyperreaction.

Fortunately, only 4 persons had to be regarded as hypertensive when the high blood pressure (145 systolic and 90 or more diastolic) and the strong ice reaction were taken as the important factors.

If discussion is restricted to the data on those whose blood pressure level is 130 systolic and 85 diastolic or lower, about 65 per cent of the total group, and further to those whose ice reaction is normal or slightly hyperreactive, such persons may be regarded as normal, though repetition of the examination of the hyperreactive persons would be desirable in order to consider the possibility of potential increase in blood presure.

The chart of the blood pressure levels (chart 1) is especially notable because of the relatively high diastolic pressure during exercise (20.8 per cent of the total above 95 mm.) and the high average diastolic ice reaction (17.4 mm. of mercury), which do not combine to make working efficiency on an optimal physiologic basis even though the values were found in the older age groups. Apart from the causes, the picture is gloomy if the condition persists, leading eventually to a higher percentage of hypertonicity.

Juvenile Vasolability.—As stated in the course of this paper, the series included more young persons than older ones, two thirds of the test subjects being 15 to 38 years of age. Our data show a particular increase in systolic blood pressure in persons 18 to 25 years of age, whereas in the older persons (above 40 years old) the difference between our figures and the American values cannot be called significant. The average rest blood pressure of 131.6 mm. of mercury for these

younger persons was above the general normal level, while in the selected group the average of 127.2 mm. was not only above that of the total group, but also above that of the American workers (Hunter and Frost, Symonds, Robinson and Brucer) who gave about 122 mm. as the highest average value for that age group. According to modern views abroad, the maximum limit for a normal rest blood pressure is 125 mm.

Chart 1 shows that the fluctuating systolic blood pressure is equalized more than the diastolic pressure, with no particular deviations in its rest value, so that the latter remains within the limits determined by us and other authors. Since the normal systolic level is about 130 mm., this juvenile group was within the uppermost limit of normal, though we admit that the level is on the high side. May and Olivier (1935) [33] classified such young persons under the heading *"hypertensions des déséquilibrés neurovégétatifs."* However, these test subjects must not be called hypertensive, but hyperreactive. A few observations from the present investigation may emphasize these conclusions:

A. The fact that the general average of this age group (18 to 25 years) approximated the ceiling limit of the physiologically optimum blood pressure level was due for the most part to those levels above 130 mm., the percentage of such levels for the age group 20 to 24 years amounting to as much as 43.5 per cent.

B. On activity, diastolic values are normally found to lie below the initial values, whereas a large number in this series needed more than one and one-half minutes for return to the original blood pressure after exercise.

C. The ice reaction pointed to an increased reactivity as shown by the high percentage of hyperreactors. Especially the diastolic reaction was high. This might be attributed to the fact that the test was performed in a sitting position, but, according to Hines, the systolic reaction should also have increased although no such increase was seen in our material.

D. Especially in the juvenile group a so-called overshooting in systolic blood pressure after the ice reaction, a fall to below the initial value, was observed; this condition certainly bespeaks a certain amount of vasolability.

E. With a high ceiling value, the blood pressure does not rise above 145 systolic and 90 to 95 diastolic and no correlation could be found between this strong reaction and the initial work measurement. However, especially the group 15 to 19 years old showed an exceedingly

33. May, E., and Olivier, J.: The Prognosis of Hypertension, Tr. Internat. Cong. Life Insur. Med., 1935, pp. 123-188.

strong pulse reaction after the ice test; for two minutes after the reaction, the pulse rate for 14.8 per cent of the total was still 4 pulsations higher, on the average, than in ice reaction, whereas normally it should not change.

If, moreover, data on this group of 18 to 24 years of age, inclusive, are placed side by side with those of Alvarez (1919),[4] the resemblance is striking. This author did not state a specific cause, though he wrote: "Some might perhaps ascribe the increase in the average pressure in 1919 to the strain of the war years, but that seems to me improbable."

Of the Dutch authors, Stokvis [34] especially emphasized the constitutional angiospastic factors which may show up as juvenile hypertension in young persons.

Later (1940), Hines pointed out the hereditary relation of hyperreactivity with high blood pressure. Hyperreactivity is also often seen in persons living under increased nervous tension. In this stronger reaction to a stimulus, as shown by the cold test, physiologic effects play a principal part, since emotional influences may be superimposed on a primary, vasomotor vascular reflex in the periphery. This reflex is imposed by central autonomic influences, which, on a possible constitutional basis, may be greater for an exogenous stimulus.[35]

The words of Robinson and Brucer [7] also proved that at normal increase in blood pressure on exogenous stimulus in youth is a frequent phenomenon, so that in America "about 40 per cent of the adult population is hypertensive or prehypertensive." Palmer [36] concluded in 1930 that "If hypertension is found at 20 years of age, it is somewhat more likely to be found persistent after ten years than it is to develop *de novo* during the interval."

There are grounds for the presumption that Western civilization has created certain conditions which lead to hypertension in persons so predisposed. The hurried life of this age, inadequate bodily and mental rest, the continuous tension under which work is performed and, finally, the psychologic tension accompanying the war, especially for our country, the hardships imposed by the occupying power—in this case the Germans—on young adults 18 to 25 years of age create the possibility of potential hypertension for those who tend toward nervousness, vasolability and hyperreaction.

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34. Stokvis, B.: Etude de l'influence de l'hypnose sur la pression du sang, à l'aide d'une nouvelle méthode d'enregistrement automatique ininterrompu, J. de physiol. et de path. gén. **35**:691-700 (Sept.) 1937; Hypnose: Psyche en bloeddruk, Lochem, De Tijdstroom, 1937.

35. Bauer, J.: Essential Hypertension: Its Nature and Etiology, Acta med. Scandinav. **108**:18-36, 1941.

36. Palmer, R. S.: The Significance of Essential Hypertension in Young Male Adults, J. A. M. A. **94**:694-697 (March 8) 1930.

Since the war influenced those factors overwhelmingly, it is to be expected that the increase in blood pressure which is shown in so many young persons will be of a transitory nature. In the winter of our study (1943-1944) the food restrictions were not so severe as they became a year later, in the winter of 1944-1945, during which blood pressures generally showed a considerable decrease.

Increased blood pressure also appeared at the examination of conscripts for military service in the war against Japan, as observed by us shortly after the war in Europe came to an end. The significance of this observation in regard to potential hypertension should certainly not be underrated.

The problem of the juvenile hypertension is worthy of deeper study because vasolability and war conditions will increase its incidence. These are not the only factors, and it remains a question whether this higher blood pressure level will be abnormal or a subsequent process without any consequences.[37]

The significance of blood pressure is reemphasized in a statement of Robinson and Brucer.[7]

> There has been a tendency lately to belittle the taking of blood pressure, but with the generally accepted realization that at least one fifth of the population is hypertensive and bears the stigma of an ominous prognosis, the blood pressure becomes a phenomenon of great moment.

CONCLUSIONS AND SUMMARY

The principal general conclusions of this study of 250 factory workers with respect to blood pressure level, pulse rate, weight, body length, age and the results of the cold pressor test are as follows:

1. We consider normal blood pressure to be a value suitable to common living conditions at which no particular aberrations are observed, either objectively or subjectively.

2. In view of the fluctuating nature of the blood pressure, it is better to describe the blood pressure level in terms of a range rather than as a certain static average.

3. In judging a blood pressure, the diastolic pressure must be regarded as primary and should be compared with the reaction to the ice test, before appraising the systolic level.

4. Blood pressure values of 70 to 85 mm. diastolic, 100 to 130 mm. systolic and an ice reaction of 20 mm. must be accepted as normal.

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37. Rühl, A.: Ueber die Bedeutung von Blutdruckerhöhung bei Jungendlichen, Ztschr. f. d. ges. Neurol. u. Psychiat. **167**:1519-1522, 1939. Werner, M.: Labiler Blutdruck und vegetatives System: Untersuchungen an jüngeren Blutdrucklabilen, Deutsches Arch. f. klin. Med. **174**:289-299, 1932.

5. A blood pressure above 145 systolic and 95 diastolic is hypertensive or prehypertensive, especially if the ice reaction has increased above the normal limit.

6. Conditions at the levels between 130 and 145 mm. and 85 and 95 mm. of mercury are dependent on the reactivity of the person and his diastolic increase, which together enable one to judge of potential hypertension.

7. The initial blood pressure measurements, determined as work, activity and ice reaction values, together with age, body length, weight and pulse rate in relation to the rest blood pressure, are, both separately and jointly, necessary for judging decisively the blood pressure level, especially when there exists any doubt as to a favorable prognosis in regard to a beginning or potential hypertensive condition.

8. A normal pulse pressure is situated between 20 and 60 mm. of mercury with a prevailing difference of pressure of 40 mm.

9. A normal pulse frequency varies in rest from 60 to 85 pulsations per minute, with 72 as an average.

10. At an average of 127.6 to 131.4 mm. systolic and 85.9 to 86.7 mm. diastolic, the values found in this group of factory workers are somewhat on the high side of the normal ranges.

11. The juvenile group of 15 to 25 years of age, comprising more than half of the material, reacted strongly on exogenous stimulus such as ice. This reaction was perhaps due to an increased psychologic state of tension, as shown by vasolability, which probably was caused by the events of the war.

12. Correlations between rest blood pressure, body length and weight proved not to be convincing, owing to the dominating factor of emotion, which was also present during the cold pressor test.

13. During the cold pressor test emotional influences may strengthen the primary peripheral and neurogenic vascular reflex. Moreover, emotion works more strongly when the vasolability has been increased by central autonomic influences, generally on a constitutional basis.

14. It is not possible to live on too high or too low a vascular tension without experiencing the consequences in the long run. Both are unphysiologic, irrational and uneconomical for maintaining the normal function of the organs and work conditions.

Minervalaan 16.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1948

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ADOLF MEYER is the last of the distinguished group that brought about the crucial psychiatric developments at the beginning of this century. In the early nineties he was thinking about the dynamics of mental disorders. The publication of William James's "Principles of Psychology" in 1892 gave support to his theories. In 1894 there appeared, in his writings on child psychology as part of the study of life, his "genetic-dynamic" approach to the understanding of mental derangement in adults. Psychogenesis was to him an obvious part of the etiology of mental disease. When he went to study under Kraepelin at Heidelberg, Germany, in 1896, he was dismayed to find psychology snowed under by nosology. Back in America he found congenial minds in Stanley Hall, William James and Morton Prince. German psychiatry was fixed in an academic rut of dualistic thinking and nosologic preoccupation. Freud was working on psychogenesis in Vienna, but he was practically alone in the German world and as yet unknown. In Worcester, Mass., in 1897, Meyer read a paper which gave a preview of his psychobiology of later years. He spoke of studying the person by various methods, all living and therefore biologic. The genesis of the disorder was to be understood by knowing what had happened to the person. "All life is reaction." . . . "Not all reactions become conscious." . . . "We cannot afford to disregard any side of the biological unit in the patient." . . . "A mental disease is a disorder of the person": These remarks show that the ideas which later made Meyer a great figure in psychiatry were well formulated at that early date. His long fight for the establishment of a dynamic psychology was not won for another twenty years. Forty years later physicians were ready to take up the holistic approach and develop psychosomatic medicine. All this history, and much more, is given in the new book just published under the title "Commonsense Psychiatry."[1] The editor, Alfred Lief, is not a physician.

1. Meyer, A. F.: Commonsense Psychiatry: Fifty-Two Selected Papers, edited, with biographical narrative, by A. Lief. New York, McGraw-Hill Book Company, Inc., 1948.

He has done his work extremely well, evidently with the help of Dr. Meyer. The book is a happy combination of well chosen, long quotations from Meyer's papers and of biographic material, worked in chronologically. It is a handsome volume, well illustrated and scholarly. The medical profession has long waited for an authoritative exposition of Adolf Meyer's contribution to medicine. This book is a satisfying answer to that wish.

Another important book which reviews a large part of a professor's lifework is Kurt Goldstein's "Language and Language Disturbances." [2] In this book are summarized not only the symptoms of aphasia but also their broad significance for medicine and in the theory of language. Goldstein disagrees with the classic theory of localization. Instead of asking, "Where is a definite symptom localized in the brain?" he would ask, "How does a definite lesion modify the function of the brain so that a definite symptom comes to the fore?" His new concept of localization depends on the recognition of cerebral symptoms as consequences of a diminution of function of the gray matter, which finds its expression in a diminished differentiation of performance. The most abstract and highly skilled performances are the most differentiated; they were the most difficult to acquire; they are the most easily lost. Thus, "a lack of special performance in one field does not appear any more as due to a special localization of a lesion but due to a particular degree of dedifferentiation of the function of the involved area." Besides discussing these general principles, Goldstein brings together a wealth of interesting information concerning language and its disorders, from dysarthria to the disturbances of intelligence in patients with aphasia. Abnormalities of reading, writing, calculating and musical recognition are especially interesting. The effects of aphasia on polyglot persons is the subject of a fascinating chapter. This is a book for the shelf of every one who is inquisitive as to how the brain works.

A remarkable monograph on headache by Harold G. Wolff [3] brings together his many investigations in that field. For years, and with many able colleagues, he has labored at the elucidation of this commonest of symptoms. Now headaches which used to be treated empirically can be attacked logically, for many causal mechanisms have been proved and many theoretic causes substantiated or disproved. Wolff made a careful study of the pain-sensitive structures in the head. The results are based largely on a long series of experiments in which

2. Goldstein, K.: Language and Language Disturbances, New York, Grune & Stratton, Inc., 1948.

3. Wolff, H. G.: Headache and Other Head Pain, New York, Oxford University Press, 1948.

these structures were explored, often by courageous neurosurgical procedures. Headache was found to originate in such diverse structures as irritated muscles, dilated blood vessels, inflamed meninges, stretched dura or distorted venous sinuses. One hundred and forty pages are given to discussion of the migraine syndrome; the vascular disorders causing the pain of migraine are described, and there is also a thorough discussion of the personality problems involved. The book performs many services for general medicine; it gives careful explanation and data concerning obscure cephalalgias; it explodes such common fallacies as "constipation headache from intestinal absorption."

From Caspersson's laboratory, in the Caroline Institute in Stockholm, Sweden, comes an intriguing publication of 117 pages, by Hyden and Hartelius.[4] With the use of the ultraviolet microscope cytochemical studies were carried out on nerve cells taken from living brain, first in animals and then in human patients undergoing lobotomy. Material from 10 patients with schizophrenia and 1 patient with chronic depression was used. As controls, 4 human brains were obtained in cases of accidental death in which postmortem examination was possible within three or four hours. In the brains of chronically psychotic patients, pyramidal cells from the frontal cortex showed a lack of polynucleotides in their cell bodies, and protein substances were in small concentration as compared with the controls. If reliable new methods have at last been found for recognition of pathologic changes in the brain of schizophrenic persons, a great advance has indeed been made. Corroboration is needed. The work with malononitrile is less convincing. Because this drug was observed to increase the content of nucleic acid and protein in nerve cells, it was given by Hyden and Hartelius to schizophrenic patients. The results at the time of this report are disappointing. Caspersson,[5] in the Salmon Lectures in November 1948, gave a more detailed description of the work.

CYBERNETICS

Two contributions in 1948 brought to neurologists and psychiatrists a summary of work that has been going on for several years. Wiener[6] has written a challenging book on cybernetics (from the Greek word for "steersman"), a discussion of "Control and Communication in the

4. Hyden, H., and Hartelius, H.: Stimulation of the Nucleoprotein-Production in the Nerve Cells by Malononitrile and Its Effect on Psychic Functions in Mental Disorders, Copenhagen, Ejnar Munksgaards Forlag, 1948.

5. Caspersson, T.: Salmon Lectures, New York, New York Academy of Medicine, to be published.

6. Wiener, N.: Cybernetics, Technology Press, New York, John Wiley & Sons, Inc., 1948.

Animal and the Machine." Northrop[7] has published in *Science* a chapter from his book "Ideological Man in His Relation to Scientifically Known Man." These two sources, with the papers by McCulloch and Pitts[8] and a review by Brazier,[9] are the principal source material for this review. As in most such developments, the earlier workers understood incompletely the implications of their observations and conclusions, but in the last five years the work has been coming rapidly to a focus; the researches of McCulloch and Pitts have produced a concept of a cerebral mechanism which could explain memory, purpose and the existence of "universals." The lack of a satisfactory explanation for these three faculties by neurologists, physiologists and psychologists has long been the main support of those who hold that man is dual in nature and that "mind" is metaphysical. The results for neurology and psychiatry will be revolutionary if further experiments support these provocative contributions.

Sherrington, with all his great knowledge of the nervous system, could not explain memory and purpose, because his concept of integration was noncircular. Says Northrop[7]:

> . . . there were no circular paths within or through the nervous system, a signal (i. e. the firing of a neuron) at any point within it could signify only what happened at a particular instant; there could then be neither purpose nor memory, and every action would be a response to a mere particular.

It was Alexander Forbes, a pupil of Sherrington, who in 1922 first suggested the existence of reverbrating circuits in networks of neurons. In a discussion of after-discharge from spinal neurons,[10] it was stated:

> The result of setting an elaborate network of this sort in action would be to establish an apparently continuous or sustained state of activity, even though in each individual conducting path the disturbance consisted of an intermittent series of transient nerve impulses. If the after-discharge depends on the

7. Northrop, F. S. C.: Neurological and Behavioristic Psychological Basis of the Ordering of Society by Means of Ideas, Science **107**:411, 1948.

8. (*a*) McCulloch, W. S., and Pitts, W.: Logical Calculus of Ideas Imminent in Mental Activity, Bull. Math. Biophysics **5**:115, 1943. (*b*) McCulloch, W. S.: Heterarchy of Values Determined by the Topology of Nervous Nets, ibid. **7**:89, 1945. (*c*) Pitts, W., and McCulloch, W. S.: How We Know Universals: Perception of Auditory and Visual Forms, ibid. **9**:127, 1947. (*d*) McCulloch, W. S., and Pitts, W.: Statistical Organization of Nervous Activity, Biometrics **4**:91, 1948.

9. Brazier, M. A. B.: Neural Nets and Integration of Behavior, in Perspectives in Neuropsychiatry, London, H. K. Lewis & Co., Ltd., 1949.

10. Forbes, A.; Cobb, S., and Cattell, H.: Electrical Studies in Mammalian Reflexes: Immediate Changes in Flexion Reflex After Spinal Transaction, Am. J. Physiol. **65**:30, 1923.

opportunity for reverberation of nerve impulses in the great network of available paths in the central nervous system, it would not be surprising to find this persistent activity greatly reduced in amount by spinal transection which isolates the local centers from those extensive tracts leading to the hind-brain and cerebellum.

Memory.—In 1933 Lorente de Nó [11] published some of his early work describing reverberating circuits histologically and physiologically. His remarkable investigations in this field led to the monograph of 1947 [12] and provided the data needed by McCulloch, Wiener and the other mathematically minded investigators of the problem. Several neurologists had used the concept of reverberating circuits to explain involuntary motor phenomena,[13] emotions [14] and anxiety, but it remained for Wiener to see that here was a fundamental explanation of memory. He is the designer of one of the great electronic computing machines, and it was he who saw the resemblance between such a machine and the central nervous system of animals. The essential fact is that a neuron circuit can be set in action by an incoming single impulse and that the circuit may go on reverberating as long as metabolism supports it, or until other incoming impulses change it. Wiener [6] states that in his computing machine "it is perfectly possible, for example, to cause any message going into storage to change in a permanent or semipermanent way the grid bias of one or of a number of vacuum tubes, and thus to alter the numerical value of the summation of impulses which will make the tube or tubes fire."

A simple example of what might happen in a computing machine constructed of banks of circuits of electronic tubes is this: At an early stage in the operation the result of a computation would set a circuit in operation in such a way that when a certain signal was transmitted it would shunt the next message into a series of circuits that would extract the square root. At the input this circuit would "decide" whether or not to accept each arriving signal. When the decision was to accept the signal, the input would work so that the resistance to the output would be lowered to the appropriate value

11. Lorente de Nó, R.: Studies on the Structure of the Cerebral Cortex, J. f. Psychol. u. Neurol. **45**:381, 1934.

12. Lorente de Nó, R.: Study of Nerve Physiology, Studies from the Rockefeller Institute for Medical Research, New York, 1947, vols. 131 (pt. 1) and 132 (pt. 2).

13. Kubie, L. S.: Excitation Waves Which Move in Closed Circuits, Brain **53**:166, 1930.

14. Cobb, S.: Borderlands of Psychiatry, Cambridge, Mass., Harvard University Press, 1943.

and the message would be shunted into the desired circuit, in this case the one that would extract the square root. In this machine, then, one has a mechanism that can be set to act in a certain way when certain circumstances arise. One circuit is set to modify the behavior of the others in response to a certain signal. The circuit stores that reaction; it has been set, i. e., it has experienced certain manipulations, and the setting manipulations are the essential past experience. Thus, the appropriate affirmative signal causes the circuit to act in the light of past experience and perform its special function.

A tube can be so changed by incoming impulses that it can act, for the rest of that run on the machine, by its stored effect and influence the manner in which the rest of the machine will transmit information. Wiener [6] states:

> In the nervous system the neurons and the synapses are elements of this sort, and it is quite plausible that information is stored over long periods by changes in the thresholds of neurons; or, what may be regarded as another way of saying the same thing, by changes in the permeability of each synapse to messages. Many of us think, in the absence of a better explanation of the phenomenon, that the storage of information in the brain can actually occur in this way. It is conceivable for such a storage to take place either by the opening of new paths or by the closure of old ones.

After a run, the computing machine is cleared and can be used for another problem. In the living nervous system a lifetime is the period of the run. In the machines the information received in a storage unit need not be used at once, but may be delayed and used at some future time. Moreover, the operation of the automaton is susceptible to change on the basis of data which have passed through its receptors in the past.

Brazier [9] sums up the matter thus:

> The importance of self-re-excitation is the influence it has on the thresholds of the synapses; it may so facilitate the incoming sensory impulses (which alone might be ineffective) as to make them now effective. This describes training. And the reverberation once started, can continue indefinitely provided the necessary energy for nerve cell metabolism is maintained, so that impulses are retained and persist through time. This last sentence is a description of memory—memory, the old puzzle of the Dualists who met the difficulty by alloting it to a non-material, non-physiological mind.

Purpose, Teleology and Feed-Back.—In my review for 1947,[15] feed-back and the original paper of Rosenblueth, Wiener and Bigelow were discussed briefly. The new contributions bring out the importance of feed-back even more and add new evidence in support of its consideration as a function of the vertebrate nervous system. As applied

15. Cobb, S.: Review of Neuropsychiatry for 1947, Arch. Int. Med. **81**:381 (March) 1948.

to mechanics, the theory goes back to Clerk Maxwell and the governor on the steam engine; in the last few years radar and self-aiming guns have been the conspicuous examples. As applied to the nervous system, feed-back means that the activity of the reverberating circuits is modified by the return of some of the output of the system as input. Brazier [9] gives the striking example of a man walking across a room with a shallow, oblong tray of water, trying not to spill it. The waves that form have to be compensated by a most intricate set of muscular actions (output), depending on proprioceptive and visual input.

Whenever one reaches with his hand for an object, a series of signals flows back (as with the self-pointing gun), through eye, touch and proprioceptive receptors, to inform the central mechanism how far the hand is overshooting or undershooting. The amounts of error determine the return input until the error becomes zero. Such a mechanism to control the search for a goal is called negative feed-back. It accompanies every motor act but can best be seen in pathologic conditions, such as cerebellar ataxia, where both input and output are disordered and the patient overshoots the mark, tries to correct his aim, undershoots and tries again, all at such a slow rate of action that the movements are visible. If the cerebellar disorder is great, the patient may acquire uncontrollable oscillations of the arm and hand; if it is less severe, he shows "intention tremor," the hand oscillating at first but eventually achieving the goal. The example of the cerebellar disorder is used for simplicity; a similar mechanism apparently works at higher levels, for example, in the auditory and visual cortical receiving stations.[8] In fact, all intelligent behavior would seem to depend on such predictive extrapolations.

The philosophic implication is of the greatest importance if one is dealing with a mechanism that allows for purposive behavior. A goal is aspired to, and may be reached, by means of a feed-back into a reverberating circuit. In other words, choice is acting on the basis of stored past experience (the "memory" of the closed circuit) to cause a volitional act. The ghost of "nonscientific teleology" is laid. Wiener [6] states:

> The machines of which we are now speaking are not the dream of the sensationalist, nor the hope of some future time. They already exist . . . Scarcely a month passes but a new book appears on these so-called control mechanisms or servo-mechanisms, and the present age is as truly the age of servo-mechanisms as the nineteenth century was the age of the steam engine or the eighteenth century the age of the clock. To sum up: the many automata of the present age are coupled to the outside world both for the reception of impressions and for the performance of actions. They contain sense-organs, effectors, and the equivalent of a nervous system to integrate the transfer of information from the one to the other. They lend themselves very well to

description in physiological terms. It is scarcely a miracle that they can be subsumed under one theory with the mechanisms of physiology.

Von Weizsäcker, in his book, "Der Gestaltkreis," [16] discusses time and space as related to biology. His descriptions of the specific forms of biologic acts as based on circular processes show that he was approaching the concept of feed-back from another point of view. He says that simultaneously the organism acts on the environment and the environment on the organism; thus, life becomes a sequence, not of cause and effect, but of decisions. Von Weizsäcker takes the determinisms out of biologic science.

"Universals" and Scanning.—Psychologists who have worked for years on the problems of perception, learning and intelligence have never been able to explain the recognition, by man and other animals, of objects whose identity is common knowledge to the group. In that group their recognition is universal, whether they are perceived at a distance or near at hand, and whether from above, below or a lateral direction. Visual recognition is an example: As long as the physiologic mechanism was postulated as a mosaic pattern thrown onto the external geniculate cells and transferred to the occipital cortex, no psychologist could explain how an object seen at a distance could be recognized as the same thing when seen nearby. But a rat has been shown to recognize a square by its shape even when size and shading are changed, and a man recognizes a letter of print whether it be lower or upper case, or even when it is a giant letter on a signboard; the mosaic theory of transmission of a visual pattern could not explain this. Pitts and McCulloch,[8] in working on a reading machine for the blind, showed that a scanning mechanism, such as is used in television, can scan a letter from top to bottom and compare top with middle and middle with bottom so that the relation of printed (black) area to white area is recorded electrically and can be reproduced. (In the case of the reading machine, this reproduction is in sound.) The investigators' researches led them to study the auditory and visual cytoarchitectonics of the mammalian cortex, and they present good evidence that such a scanning mechanism could be present in the cerebrum of man. In fact, the alpha rhythm of Berger would accord with the theory that scanning actually takes place in the visual cortex.

The existence of such a scanning mechanism would explain how an object is recognized when seen at various distances and from various angles. A pencil profile on paper does not look much like a man's actual face; yet it is quickly recognized. Moreover, categories appear: Men are recognized as men and birds as birds. Thus,

16. von Weizsäcker, V.: Der Gestaltkreis: Theorie der Einheit von Wahrnehmen und Bewegen, Stuttgart, Georg Thieme, 1947.

particular impressions call forth universal reaction. So far, the only mechanism known whose existence seems to explain this process is a servomechanism, in a nerve network, with negative feed-back and some sort of group scanning assembly. Theoretically, nerve circuits, synapses and nerve impulses acting according to the all or none law could act as such a mechanism as well as the electronic computing machines.

McCulloch and Pitts sum up their conclusions in their latest paper [84]:

(1) The actions of neurons and their mutual relations can be described by the calculus of propositions subscripted for time. (2) The nervous system as a whole is ordered and operated on statistical principles. Thereby it adjusts the all-or-none laws governing its elements to a physical world of continuous variation. (3) It detects universals. (4) It conserves its own level of activity, the condition of the body it inhabits, and its relation to the physical world by activity in closed paths such that a change in its output causes a change of opposite sign in its input. (5) It chooses between ends. (6) It alters its structure by experience.

The joint work of Rosenblueth, Wiener and Bigelow [17] represents the fruitful conjunction of electronic physics with neurophysiology. Great results are to be expected if the promises of this first work are confirmed in future experiments. If only one promise is realized, i. e., the explanation of memory, it will be a great day for psychology. If purpose and the recognition of universals can also be explained electrophysiologically, there will be a new epoch in research on the nervous system.

EPILEPSY

The advancing knowledge of epilepsy was signalized in 1941 by the publication of two books, "Science and Seizures," by Lennox,[18] which gave the medical aspect, and "Epilepsy and Cerebral Localization," by Penfield and Erickson,[19] which dealt with the neurosurgical aspect. The latest progress appears in Epilepsy,[20] volume 26 of the *Association for Research in Nervous and Mental Disease, Proceedings,* which appeared early in 1948

Diagnostic methods have improved, but the specialist still relies on three fundamental procedures available to the internist: first, obtain-

17. Rosenblueth, A.; Wiener, N., and Bigelow, J.: Behavior, Purpose and Teleology, Philos. of Sc. **10**:18, 1943.

18. Lennox, W. G.: Science and Seizures: New Light on Epilepsy and Migraine, ed. 2, New York, Harper & Brothers, 1946.

19. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization: A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures, Springfield, Ill., Charles C Thomas, Publisher, 1941.

20. Lennox, W. G.; Merritt, H. H., and Bamford, T. E.: Epilepsy, Proceedings of the Association for Research in Nervous and Mental Disease, Baltimore, Williams & Wilkins Company, 1947, vol. 26.

ing of a thorough and exact history, with careful description of the aura and seizures; second, a neurologic examination, with careful attention to indications of birth injury, such as asymmetry of the body structure or of reflexes,[21] and, third, repeated opthalmoscopic examination of the eyegrounds, to help exclude the presence of a brain tumor. Roentgenograms of the skull are made routinely. Lumbar puncture and pneumoencephalography are often useful.

The electroencephalograph, however, is the great new aid in the diagnosis and treatment of epilepsy. Of the 616 pages in the research volume on epilepsy,[20] approximately 200 are devoted to electroencephalography. Abbott and Schwab [22] report that about 20 per cent of persons known to have epilepsy have normal electroencephalograms when examined between seizures. Patients in this group with normal tracings have less severe epilepsy and show better response to medication than the 80 per cent of patients with any abnormality of the tracings. Erna and Frederic Gibbs [23] write that they have found that the tracings of 36 per cent of epileptic patients contain "seizure discharges" between clinical seizures. These brief episodes of high voltage slow or fast waves resemble the discharges seen during an epileptic seizure. The Gibbses observed that the seizure discharges occurred in 82 per cent of their patients during sleep, in contrast with their occurrence in 36 per cent of patients while awake. The authors believe that taking the electroencephalograph on sleeping patients is a more effective way of proving the presence of epilepsy than the more difficult technics of hydration, hypoglycemia or injection of metrazol.® Kaufmann, Marshall and Walker [24] made especial use of the metrazol® method in the localization of focal cerebral lesions. Two hundred milligrams of metrazol® was slowly injected intravenously while an electroencephalographic record was being made. The patients, in an Army hospital, had traumatic epilepsy. In 44 per cent of patients the focus of cerebral irritability showed itself on the first trial. Repeated examinations brought out the focus in 30 per cent of the others. The injection caused clinical seizures in 14 per cent of patients.

21. Penfield, W., and Robertson, J. S. M.: Growth Asymmetry Due to Lesions of Postcentral Cerebral Cortex, Arch. Neurol. & Psychiat. **50**:405 (Oct.) 1943.

22. Abbott, J. A., and Schwab, R. S.: Normal Electroencephalograms in Patients Having Proven Epilepsy, A. Research. Nerv. & Ment. Dis., Proc. **26**: 332-338, 1947.

23. Gibbs, E. L., and Gibbs, F.: Diagnostic and Localizing Value in Electroencephalographic Studies in Sleep, A. Research Nerv. & Ment. Dis., Proc. **26**: 336-366, 1947.

24. Kaufmann, J. C.; Marshall, C., and Walker, A. E.: Metrazol Activated Electroencephalography, A. Research Nerv. & Ment. Dis., Proc. **26**:476-486, 1947.

Another, and more certain, method of localization is use of the "electrocorticogram," an electroencephalogram made directly from the cortex exposed at operation. Walker and his associates [25] found spontaneous focal electrical alterations in 14 of 39 explorations. Stimulation of the cortex with a current insufficient to cause clinical symptoms will almost always induce a focal spike discharge in the presumably epileptogenic area, the area to be excised. The exploring electrode has even penetrated the depths of the human brain. Spiegel and associates [26] and the Gibbses [28] have recorded waves simultaneously from the cortex and the region of the thalamus.

During the transient blackout of consciousness called petit mal, high voltage, 3 per second waves appear on the electroencephalogram, each wave preceded by a sharp spike. This discharge is widespread and bilaterally symmetric and synchronous. This "dart and dome dysrhythmia" is confined almost wholly to patients with a history of one or more of the triad: petit mal, myoclonia and akinetic fits. Such seizures are especially common in children and are not to be confused with mild convulsive fits or with brief periods of amnesia or automatism. Lennox [27] designates them as the "petit mal triad," an important clinical segregation; I should call the group the "dart and dome triad," since that is the electroencephalographic characteristic of all three disturbances and because the short, choreic jerks of myoclonia and the flaccid fall of the akinetic fit often occur without the typical short mental lapse of petit mal.

Penfield, who stated in a previous work with Erickson [19] that this form of seizure probably originated in the diencephalon in man, now states with Jasper [28] that they have experimental evidence that there is a "pacemaker" for the brain waves in the medial parts of the thalamus. So long as this area is stimulated by brief, rhythmic electric shocks at the rate of 3 per second, the electroencephalographic pattern typical of petit mal appears from electrodes placed on the cortex. This work is important because it gives insight into the mechanism of genetic epilepsy, as against traumatic epilepsy. I do not use the old term "idiopathic" because I agree with Lennox, the Gibbses and others that the term, always a cloak for ignorance, is outmoded. A characteristic of certain types of genetic (hereditary)

25. Walker, A. E.; Marshall, C., and Beresford, E. N.: Electrocorticographic Characteristics of Cerebrum in Posttraumatic Epilepsy, A. Research Nerv. & Ment. Dis., Proc. **26**:502-515, 1947.

26. Spiegel, E. A.; Wycis, H. T.; Freed, H., and Lee, A. J.: Stereoencephalotomy, in Program of the American Neurological Association, 1948, p. 46.

27. Lennox, W. G.: Petit Mal Epilepsies: Their Treatment with Tridione. J. A. M. A. **129**:1069 (Dec. 15) 1945.

28. Penfield, P. W., and Jasper, H. H.: Highest Level Seizures, A. Research Nerv. & Ment. Dis., Proc. **26**:257-271, 1947.

epilepsy seems to be bilateral symmetry and synchronism of the cortical waves. The work of Jasper and Penfield points to the thalamus as the area of origin of these abnormalities of electroencephalographic rhythm.

Gibbs, Gibbs and Fuster [29] have discovered that diphasic or positive (downward pointing) spike discharges are usually present in the leads from the scalp over an anterior temporal area if the patient is asleep and if he has a history of automatism, called by the authors "psychomotor" seizures. Surgical exploration, made in a number of cases, has disclosed a lesion at the temporal pole. Electrocorticograms made at operation have corroborated the preliminary diagnosis made from tracings taken from electrodes placed on the scalp. The frequency of spike foci at the temporal pole may be due to blows to the skull that bruise the tip of the temporal lobe, for example, injury to the occiput from a fall backward, from contrecoup or from a punch on the jaw.

Causes of Epilepsy.—The new diagnostic methods throw light on the probable causes of epilepsy. Certainly, etiologic diagnosis would be more satisfactory than the confused nomenclature now in use. With greater knowledge, epilepsy might be classified as genetic, traumatic, infectious, neoplastic and degenerative in origin. The genetic group is much the largest, comprising probably about 75 per cent; a genetic factor may underlie even the form deemed traumatic. Lennox and his co-workers [30] have shown the importance of this hereditary factor in studies of twins and, with the use of the electroencephalograph as a diagnostic instrument, in the study of parents and other close relatives of epileptic patients. Migraine is often associated with epilepsy, both clinically and genetically. Epileptic persons have an inordinately large number of migrainous ancestors.[18] Migraine may not always be a pain in the head; abdominal migraine has long been known, and Moore [31] has recently described this syndrome as "abdominal epilepsy." Paroxysmal abdominal pain that cannot be explained may yield to a therapeutic trial with diphenylhydantoin sodium (dilantin sodium®). The electroencephalogram may be abnormal.

According to Lennox, epilepsy after trauma is most likely to develop in persons with an inherited cerebral dysrhythmia. However, age

29. Gibbs, F. A.; Gibbs, E. L., and Fuster, B.: Anterior Temporal Localization of Sleep-Induced Seizure Discharges of Psychomotor Type, Tr. Am. Neurol. A. **72**:180, 1947.

30. Lennox, W. G.: Sixty-Six Twin Pairs Affected by Seizures, A. Research Nerv. & Ment. Dis., Proc. **26**:11-34, 1947.

31. Moore, M. T.: Abdominal Epilepsy, Rev. Gastroenterol. **15**:381, 1948.

and extent of damage are important factors. Quadfasel and Walker [32] found that heredity was of little importance in the development of epilepsy in 246 soldiers with penetrating wounds of the brain.

Wartime trauma is an especially important factor just now, with the great number of patients with epilepsy in hospitals of the Veterans Administration. In civilian life birth trauma and automobile accidents are the commonest causes. Trauma may lead to focal cerebral infection with abscess formation, and the resulting scars may cause epileptogenic foci in the brain. Encephalitis of other kinds is a less common cause of epilepsy.

Tumors of the brain are also important. In the series of 160 cases reported by White, Liu and Mixter,[33] seizures occurred in 1 out of 3. On the other hand, of 1,130 patients with epilepsy, 240 (21 per cent) had focal lesions, of which only 160 (14 per cent of all patients in the series) had tumors. In the 595 cases reported by Hoefer and his associates,[34] astrocytoma was the tumor most frequently accompanied with convulsions.

Congenital cerebral aplasia and degenerative diseases of the brain commonly are acompanied with fits. Patients with these conditions fill the beds of epileptic colonies and hospitals for the feebleminded. They form a veritable museum of neurologic curiosities, but the epilepsy might be called incidental, being secondary to the cerebral lesions. Although many of these patients have hereditary degenerative diseases of the brain, such as Friedreich's ataxia and tuberous sclerosis, their conditions are not to be confused with the genetic epilepsy already discussed.

Treatment.—It is in the field of treatment that the greatest advances have been made. Before the more clinical papers are discussed, mention should be made of the review written by Toman and Goodman [35] from a pharmacological standpoint; it gives an excellent basis for the understanding of the recent therapeutic advances.

Surgical removal of epileptogenic foci has been facilitated by the use of the electrocorticogram at operation. The exploring electrode is used to identify not the gross lesion but the actual focus of abnormal

32. Quadfasel, F. A., and Walker, A. E.: Problems of Posttraumatic Epilepsy in an Army General Hospital, A. Research Nerv. & Ment. Dis., Proc. **26**:461-475, 1947.

33. White, J. C.; Liu, C. T., and Mixter, W. J.: Focal Epilepsy: Epilepsy Secondary to Intracranial Tumors, New England J. Med. **238**:891, 1948.

34. Hoefer, P. F. A.; Schlesinger, E. B., and Pennes, H. R.: Seizures in Patients with Brain Tumors, A. Research. Nerv. & Ment. Dis., Proc. **26**:50-58, 1947.

35. Toman, J. E. P., and Goodman, L. S.: Anticonvulsants, Physiol. Rev. **28**:409, 1948.

neural irritability.[25] It may be more important to remove the slightly atrophied cortex near a cicatrix than the visible scar itself.[37]

Medical treatment has been aided greatly by the development of new drugs that have more specific action than those previously used. Instead of using bromides and phenobarbital for the treatment of all types of fits, the therapeutist can now use the oxazolidine derivatives, such as trimethadione (tridione®) for treatment of the "petit mal triad" and diphenylhydantoin sodium U. S. P. (dilantin®) for psychic seizures. Phenobarbital U. S. P. remains the mainstay for treatment of all types of epilepsy, especially major convulsions. It should be given at night; if administration of divided doses is indicated during the day as well, diphenyl hydantoin sodium is preferable, as it causes much less drowsiness. A commonly effective combination for an adult is 0.1 Gm. of phenobarbital at bedtime combined with 0.1 Gm. of diphenyl hydantoin sodium three or four times a day after meals.

In some patients swollen gums or staggering gait may develop as a reaction to excessive amounts of diphenyl hydantoin. With such patients, or when diphenyl hydantoin is not fully effective, mesantoin® (3-methyl-5, 5-phenylethylhydantoin) may be substituted, often with surprisingly good effect. A dose larger than that of diphenyl hydantoin can usually be tolerated, the chief limiting factor being somnolence. Rash may be troublesome, and the blood should be examined monthly for evidence of neutropenia. Trimethadione, which is so effective for the "dart and dome triad" in children, may cause neutropenia and agranulocytosis, so the blood must be examined once a month. The drug also often causes a sensation of glare (day blindness) when the person is exposed to sunlight. The analogue paradione® (3, 5-dimethyl-5-ethyl oxazolididine-2, 4-dione) is less likely to cause disturbing side effects, but is somewhat less effective in the treatment of petit mal. Phenacetylurea (phenurone®) is another new drug sometimes useful in the treatment of both petit mal and psychic seizures. Side effects may be psychic excitement, insomnia or dermatitis. Rashes are not rare in patients taking any of these preparations.

Treatment of epilepsy with bromides is obsolete. The word "bromide" does not even appear in the index to the new volume on epilepsy![20]

Among the adjuvants to the drugs listed in the accompanying table, caffeine is in first place; it is especially useful with trimethadione in control of myoclonic jerks, especially those that occur in the morning before breakfast. Strong coffee in a thermos bottle at

36. Footnote deleted.

37. Penfield, W.: Posttraumatic Epilepsy, Am. J. Psychiat. **100**:750, 1944.

the bedside is a great help. Both coffee and d-amphetamine sulfate (10 to 30 mg.) (dexedrine®) may be used to relieve the drowsiness caused by phenobarbital, N-methyl phenobarbital (mebaral®) or mesantoin.® Glutamic acid hydrochloride (5 to 20 Gm. per day) is said to improve mental efficiency.[38] It was tried, but was found wanting as an anticonvulsant. Electric shock has been tried[39]; use of such a homeopathic remedy should be most cautious. In the dangerous, clouded states of epilepsy or in the depressed and moody prodromes to a convulsion, electric shock may prove to be a useful adjuvant.

For the emergency of status epilepticus the treatment most usually effective is administration of phenobarbital sodium intravenously, in

Treatment of Epilepsy with Various Drugs

Drug	Daily Dose, Gm.	Use	Bad Effects
Barbiturates *			
Phenobarbital U. S. P.....	0.1 to 0.3	All types of epilepsy	Drowsiness, rash
"Mebaral".....	0.2 to 0.4	Petit mal	Drowsiness, rash
Hydantoin derivatives			
"Dilantin".....	0.3 to 0.6	Convulsions and psychic seizures	Gingivitis, ataxia
"Mesantoin".....	0.3 to 0.8	Convulsions and psychic seizures	Drowsiness, rash, neutropenia
"Phenurone".....	1.5 to 3.0	Psychic and psychomotor seizures	Rash, excitement
Oxazolodine derivatives			
"Tridione".....	0.3 to 0.6	Petit mal	Neutropenia, day blindness
"Paradione".....	0.3 to 0.6	Petit mal	Less neutropenia, less day blindness
Bromides.....	.....	Not recommended	Cumulative drowsiness and acne

* "Mebaral" is N-methyl phenobarbital; "dilantin," diphenylhydantoin sodium U. S. P.; "mesantoin," 3-methyl-5, 5-phenylethyl hydantoin; "phenurone," phenacetylurea; "tridione," trimethadione, and "paradione," 3, 5-dimethyl-5-ethyl oxazolididine-2, 4-dione.

doses of 0.4 to 0.8 Gm. If this method does not work, or if the soluble drug is not available, paraldehyde U. S. P. (3 to 6 cc.) may be given very slowly, intravenously. The important thing is to have the courage to give a single, large dose in the beginning.[40] Etherization by mask is necessary in the worst cases but may lead to inhalation pneumonia.

Psychologically, epilepsy is a tremendous burden for the patient. Fear is almost omnipresent: fear of the next seizure, fear of losing

38. Zimmerman, F. T.; Burgemeister, B. B., and Putnam, T. J.: Effect of Glutamic Acid on Mental Functioning in Children and in Adolescents, Arch. Neurol. & Psychiat. **56**:489 (Nov.) 1946.

39. Kalinowsky, L. B.: Epilepsy and Convulsive Therapy, A Research Nerv. & Ment. Dis., Proc. **26**:175-183, 1947.

40. Merritt, H. H.: Treatment of Epilepsy, Cincinnati J. Med. **27**:279, 1946.

social status, fear of losing a job; it may lead to a state of continuing dread.[41] Thus, the fact of suffering from epilepsy causes psychic symptoms. That psychic stimuli may precipitate seizures in a person with epilepsy is well known, but psychic states of maladjustment and tension are only precipitants of fits, not causes of epilepsy. Nevertheless, the treatment of these states of nervous tension and emotional maladjustments is an important part of therapy.[42] The administration of drugs or a surgical operation is not enough. A surprising amount of good can be done by carefully studying and treating the patient's social and psychologic difficulties.[43]

Last, but not least, patients with epilepsy must give up alcohol completely! No compromise can safely be made with this rule; too many failures come from allowing "just a little beer" or "a few drinks."

Massachusetts General Hospital.

41. Penfield, W.: Epilepsies, with Note on Radical Therapy (Sattuck Lecture), New England J. Med. **221**:209, 1939.

42. Aring, C. D.; Lederer, H. D., and Rosenbaum, M.: Role of Emotion in the Causation of Epilepsy, A. Research Nerv. & Ment. Dis., Proc. **26**:561-572, 1947.

43. Mittelmann, B., in Hoch, P. H., and Knight, R. P.: Epilepsy: Psychiatric Aspects of Convulsive Disorders, New York, Grune & Stratton, Inc., 1947, chap. 11.

Book Reviews

Parathyroid Glands and Metabolic Bone Diseases: Selected Studies. By Fuller Albright, M.D., and Edward C. Reifenstein Jr., M.D. Price, $8. Pp. 393, with 155 illustrations. Baltimore: The Williams and Wilkins Company, 1948.

There are few systems of the body that are less well understood generally than the skeletal system. The metabolism of calcium and phosphorus and the mechanism by which bones maintain their integrity are more or less taken for granted by most physicians. With the publication of this excellent book there is no longer any reason for any physician to fail to understand the principles of the physiology of the parathyroid glands and the pathologic physiology of some of the bone diseases. The material is presented in a simple, clear, didactic manner which leaves the reader no doubt concerning the views of the authors. The clinical studies which form the basis of these views have been conducted in the metabolic ward of the Massachusetts General Hospital over a period of twenty-four years.

The series of selected metabolic studies which form the skeleton, as it were, of the text illustrate clearly the important features of the diagnosis, treatment and course of metabolic bone diseases. The chapter on postmenopausal and senile osteoporosis is excellent and should be read by every physician caring for elderly patients.

Everything about this book is pleasing. The illustrations are good, and the detailed metabolic charts are remarkably clear and comprehensible. The authors have a faculty for lucid exposition, which is unusual, and the discussions of acid-base equilibrium and hormonal interrelationships are not at all confusing. The reviewer has no reservations in recommending this book for every physician's library.

Manual for Laboratory Work in Mammalian Physiology. By Fred E. D'Amour, M.D., and Frank R. Blood, M.D. Price, $2.75. Chicago: University of Chicago Press, 1948.

This is a loose leaf laboratory syllabus, profusely illustrated, dealing with fifty experiments in fundamental physiology. The white rat is the subject, and standard procedures are described. There is space after each experiment for the student's report.

Die viscerographische Methode: Menschliche normale und pathologische Physiologie und Pharmakodynamie der Motilität des Oesophagus, des Magens, des Darmes und der Blase. By D. Danielopolu. Paper. Price, 7.20 marks. Pp. 166, with 130 illustrations. Berlin: S. Karger, 1930.

This is a compilation of work published during the last ten years by the author and his collaborators. It consists of physiologic and pharmacologic experiments in normal and in diseased men. In these experiments from one to three recording balloons were passed into the esophagus, stomach, small intestines, colon or bladder. Danielopolu believes that this type of work is of great value to the clinician, but in a rather verbose discussion of the experiment he does not present much to support the statement. He feels that his experiments are of great value

also in showing how different the pharmacologic reactions of the digestive tracts are in man and in laboratory animals. Actually the kymographic records show that drugs act much the same in animals and in man. The striking fact that the clinician should note is that most of the actions of drugs were fleeting. The physician when he gives a drug hopes to secure an action that will last several hours. Danielopolu's records show that the effects usually last seconds or minutes; it is often a mixture of inhibition and stimulation, and this mixture varies with the dosage used. The book really constitutes a valuable and unusual contribution to the knowledge of the motor functions of the digestive tract. There is much of interest about the behavior of the esophagus, stomach and bowels. It is interesting to see that atropine and physostigmine appear to sensitize the gastric musculature so that it will react more markedly to psychic stimuli. The esophagus in cases of cardiospasm appears to contract peculiarly. Large doses of ephedrine appear to quiet the intestine for several minutes. Pilocarpine produced a temporary increase of gastric motility followed by a period of quiet. The effect of epinephrine lasted only a few seconds. Small doses of atropine seemed to increase the activity of the stomach, but large ones inhibited it. The book should be studied by everyone who is interested in the research side of gastroenterology.

The Skull, Sinuses and Mastoids: A Handbook of Roentgen Diagnosis. By Barton R. Young, M.D. Price, $6.50. Pp. 328, with 373 illustrations. Philadelphia: Year Book Publishers, 1948.

This comprehensive little atlas of roentgen diagnosis of the skull, sinuses and mastoids seems to cover the subject in excellent fashion. Each of the 140 plates is on the right hand page and opposite on the left is the text discussion conveniently placed. Pictures of the normal skull and sinuses are followed by plates illustrating disease conditions. The reproductions are adequate and in many cases excellent. There are a bibliography and an index. The reviewer is impressed by the usefulness of this series of monographs not only to the radiologist but to the general physician.

Clinical Laboratory Methods and Diagnosis: A Textbook on Laboratory Procedures, with Their Interpretation. Volumes 1, 2 and 3. By R. B. H. Gradwohl, M.D. Vol. III: (Vol. 3 by R. B. H. Gradwohl and Pedro Kouri). Price, $32.50 (Vols. 1 and 2); $15 (Vol. 3); set, $40. St. Louis: C. V. Mosby Company, 1948.

This monumental work includes in its three volumes descriptions of all the "laboratory procedures" used in ordinary clinical practice; one finds here conveniently brought together material which usually must be sought in various books. Dr. Gradwohl's vast experience guarantees one's confidence, and it is a pleasure on turning through these pages to find what an excellent and comprehensive job has been achieved. One cannot review in detail such a mass of material; suffice it to say that the descriptions of the various procedures are given in full and are profusely illustrated with cuts and tables. In a book of this sort it is hardly to be expected that the selection of material could be perfect, and in the approach to completeness occasional obsolete or useless tests are included. This is especially to be noted in the discussion of gastric analysis, which is mainly a repetition of the old procedures which have little application in present day practice. On the whole, however, one is amazed at the completeness and excellence of this vast compendium. The innumerable illustrations of every conceivable sort, the many tables, the references to the literature and the general excellent get up of the books are especially to be commended.

Biology of Disease. By Eli Moschcowitz, M.D. Price, $4.50. Pp. 221. New York: Grune & Stratton, Inc., 1948.

This is an interesting volume made up of chapters on a number of interesting diseases, twenty-four in all. Some of the subjects are hypertension of the pulmonary circuit, periarteritis nodosa, Libman-Sacks disease, polycythemia vera, follicular lymphoblastoma, myeloma, the relation of neurocirculatory asthenia to exophthalmic goiter, toxic hepatitis, obesity, peptic ulcer, achlorhydria in relation to anemia, cardiospasm, sprue syndrome, emphysema, psychosomatic medicine, nephrosis and the hyperkinetic diseases. A number of these articles have been published before.

Moschcowitz starts with the idea that many diseases are not sharply defined genera but transitions of morbid states from one to another. Sir Thomas Lewis had the idea that sometimes when physicians separate one disease from another with the help of refined methods they do themselves a disservice. They rather confuse things. "It would be just as consistent to classify the earliest, the intermediate, and the final phases of disease as separate entities as it would be to classify the tadpole and the frog as different species."

Much of the confusion in classifying diseases is, of course, due to ignorance of the real causes. Some diseases are probably due to mutations. Unfortunately, the physician who practices in a big charity hospital sees too much of the end phases of disease. What is much needed in medicine today is a study of certain diseases throughout the patient's lifetime. As Osler once said, the bronchopneumonia that killed him was only an episode in a disease which had been threatening him from the time he was a young man. There is need also today for following the manifestations of some so-called diathesis through the many members of a family. For instance, it is probably more than a coincidence if one finds a man suffering from pernicious anemia and his nephew suffering from acute leukemia or myeloma.

In the volume here reviewed, Dr. Moschowitz' main purpose was to stimulate a point of view and a methodology and to emphasize a dynamic as opposed to a static approach to the study of disease. As one would expect, there is a tremendous amount of material in this book that is most thought stimulating, and every studious internist or physician in any specialty will do well to read it. It is a good book to put by the side of one's bed to read for a half hour each night before going to sleep.

Practical Bacteriology, Hematology and Parasitology. By E. R. Stitt, M.D. and others. Tenth edition. Pp. 991. Philadelphia: The Blakiston Company, 1948.

The popularity of this book among members of the medical profession is attested by the fact that it is now in its tenth edition. Because of the ever increasing number of laboratory procedures employed in clinical medicine, the book is increasing in size and scope. The number of persons, expert in their respective fields, who contribute to the present edition has increased.

Many new editions and revisions have been made to include the more recent developments in laboratory technics. These are too numerous to mention. The general style of the preceding edition is retained, i. e., certain pertinent clinical data are presented in an effort to correlate the laboratory technics with the practical clinical problems. The sections on bacteriology and parasitology are better developed than those chapters on hematology. As the title indicates, the book is concerned with the more practical aspects of these subjects and does not include

details of more academic interest. The book should prove of value to everyone involved in laboratory procedures as well as to those interested in some of the practical aspects of bacteriology, including mycology, parasitology and general clinical laboratory technics concerned with the study of urine, gastric contents and stools and other clinical laboratory procedures.

The Diabetic's Handbook. By Anthony Sindoni Jr., M.D. Price, $3. Pp. 194. New York: The Ronald Press Company, 1948.

The prime purpose of this book is to give the diabetic patient an intelligent and working knowledge of his disease.

The book is conveniently divided into six sections, each dealing with a separate aspect of diabetes. The first and perhaps the most valuable section as far as the patient is concerned contains a list of the questions most commonly asked by patients and their answers. The answers, as is also true for the most of the book, are written and explained in simple lay terminology. This style of writing adds greatly to the value of the book. The remaining sections cover the causes, symptoms and complications of diabetes, insulin types and insulin reactions, a simple and informative section on diabetic dietetics and a final section on the ordinary diabetic laboratory tests and information concerning the general hygiene which the person with diabetes should pursue.

Any diabetic patient of average intelligence should have no difficulty in fully understanding this book.

A-B-C's of Sulfonamide and Antibiotic Therapy. By Perrin H. Long, M.D. Pp. 231. Philadelphia: W. B. Saunders Company, 1948.

This handy-sized compendium offers a thorough summary of the principles of sulfonamide and antibiotic therapy. A general discussion of dosage schedules and clinical, pharmacologic and toxic reactions is followed by brief discussions of the various common infective diseases. In each a drug of choice, a treatment schedule and recommended auxiliary measures are presented. The recommendations are dogmatic and explicit and represent the best current opinions on the subject. This book deserves a place on every physician's desk and in every house officer's room.

Anales de la cátedra de clínica médica. By E. S. Mazzei, M.D. Pp. 367. Buenos Aires: "El Ateneo."

This book is a collection of lectures on diverse subjects of general medical interest. They have little interrelationship between themselves and appear to be a series of conferences given to students by several lecturers under the direction of the author. The subjects included are functional renal insufficiency, the syndrome of endobronchial hypertension, nonoperative treatment of chronic nontuberculous empyema, mass roentgen ray surveys, carcinoma of the common bile duct, endocranial metastases of pulmonary neoplasms and hemorrhagic pleurisies.

The bulk of the book is devoted, however, to a discussion on pulmonary embolism. This subject is extensively covered in all its aspects, including its pathogenesis, clinical features, experimental data, prevention and treatment. The bibliography is ample and authoritative, and the presentations should be of value to Latin-American students and physicians.

All these subjects are well covered in English medical literature. Thus it is felt that the book would be of little value to American physicians.

Handbook of Orthopaedic Surgery. By A. R. Shands Jr., M.D., in collaboration with Richard Beverly Raney, M.D. Third edition. Price, $6. Pp. 574. St. Louis: C. V. Mosby Company, 1948.

Dr. Shands's book has now run through several editions and has made its place as a brief and straightforward compendium of orthopedics. Good illustrations, a comprehensive bibliography and an index supplement the text. A book of this sort should be especially useful to general physicians and medical students, and, indeed, the authors state in the preface that such is their purpose.

A Course in Practical Therapeutics. By Martin Emil Rehfuss, M.D.; F. Kenneth Albrecht, M.D., and Alison Howe Price, M.D. Price, $15. Pp. 824. Baltimore: The Williams & Wilkins, Company, 1948.

In this encyclopedic volume Dr. Rehfuss and his associates have brought together a vast amount of useful information. General considerations are followed by sections on clinical pharmacology and treatment according to major symptoms, such as cough, headache and diarrhea, after which treatment of special conditions is dealt with. Everything is taken up in abstract form with the directions given in A, B, C style. Under hiccup, for example, one finds listed some seventy-five therapeutic items. While one may not agree with all that is included between these covers, the student will rarely fail to find at least some therapeutic suggestion when he is at a loss. The volume is "different" and certainly is worth while having on one's shelf for reference.

Modern Clinical Psychiatry. By Arthur P. Noyes, M.D. Third edition. Price, $6. Pp. 525. Philadelphia: W. B. Saunders Company, 1948.

This is the third edition of a book which is familiar to most psychiatrists and students in psychiatry. It is among the most widely used textbooks of psychiatry.

As the author states in the preface, this third edition has been largely rewritten. The psychodynamic principles of the psychoneuroses are discussed more fully, and there is more attention directed to the psychosomatic mechanisms. There are 32 chapters. Three new chapters have been added—"Psychotherapy," "Shock and Other Physical Therapies" and "Child Psychiatry." A bibliography follows each chapter.

The mechanisms of defense or the adjustmental mechanisms are described in the earlier chapters with such clarity that their meaning is easily applied to mental disorders as discussed in the later chapters. A brief discussion of "psychological considerations" in a few instances is stimulating, and one wishes the author had gone further with these considerations, particularly in relation to the organic reaction types of psychoses.

Medical students and students in psychiatry should find this a helpful and valuable book.

Cor pulmonale: I. Congreso Nacional de Cardiología, II. Ponencia. By J. Codina- Altés, M.D. Pp. 206, with 72 illustrations. Madrid: Libreria Editorial, Cientifico Médica Española, 1944.

This book is an exhaustive study of cor pulmonale, with references to all prominent publications on the subject, which are drawn primarily from the American literature but which include British, French and German references. In addition to a well organized and excellent condensation of the literature, Dr. Codina-Altés includes his personal observations on 97 cases.

The author discusses the subject in respect to etiology, pathogenesis, clinical, radiologic and electrocardiographic findings, clinical course, diagnosis and treatment and includes separate discussions of acute and subacute cor pulmonale. Charts and roentgenograms from many of his own cases are appended.

The Management of Obesity. By Louis Pelner, M.D. Price, $3. Pp. 144. New York: Personal Diet Service, 1946.

In this book both the endocrine aspects of obesity and the practical management of the condition of the obese patient are discussed. Many physicians do not agree with Engelbach's classification of the hypogonad, castrate, adiposogenital and pituitarothyroid types of obesity. Not all physicians will agree with the statement that "The patient should always be given a diet consisting of about 1,000 calories," since many physicians prescribe diets containing fewer calories.

Considerable attention is given to the use of drugs in the treatment of obesity. The food tables and outlines of diets consisting of 1,000, 1,200 and 1,500 calories are satisfactory. This small volume with references and index will be helpful to many physicians.

Recent Advances in Clinical Pathology. By S. C. Dyke, M.D., and others. Price, $5.50. Pp. 468. Philadelphia: The Blakiston Company, 1947.

It has become increasingly difficult for any one person to present adequately the advances in the various aspects of clinical pathology. In preparing this text on the "recent advances in clinical pathology," sponsored by the European Association of Clinical Pathologists, the editor has enlisted the aid of section editors for the four divisions of bacteriology, biochemistry, hematology and histology. These in their turn have secured the services of those best fitted to present the advances in each of their special fields. The result has been a compact but comprehensive volume, of great value not only to clinical pathologists but also to practicing physicians.

Essentials of Medicine. By Charles P. Emerson Jr., M.D., and Jane Elizabeth Taylor, R.N. Fifteenth edition. Price, $3.50. Pp. 688. Philadelphia: J. B. Lippincott Company, 1946.

The appearance of a fifteenth edition of this standard work indicates that many generations of instructors in schools of nursing have found it to be a satisfactory textbook. Economy in print and margins now makes it possible to condense an immense amount of information in an octavo volume. The general format and the many diagrams, photographs and colored plates are excellent features, and we have no doubt that the book will continue to be a leader in the field of nursing education.

Atlas of Cardiovascular Diseases. By Irving J. Treiger, M.D. Price, $10. Pp. 180, with 244 illustrations. St. Louis: The C. V. Mosby Company, 1947.

This folio volume shows on each right hand page roentgenograms, electrocardiograms and photographs of gross specimens and on the left an abstract of the case history. The material is well selected and concisely presented, and the entire range of important cardiac lesions is covered. The cuts are for the most part well reproduced. The book is an excellent summary of cardiac disease and should also be useful for quick reference.

Dentistry: An Agency of Health Service. By Malcolm Wallace Carr, D.D.S. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. Price, $1.50. Pp. 219. New York: The Commonwealth Fund, 1946.

This book is interesting reading. It contains many facts concerning dentistry presented in a clearcut, brief and concise manner. It would serve an extremely useful purpose in public and high school libraries, in which young men and women interested in professional education might have access to it.

Principles of Hematology. By Russell L. Haden, M.D. Third edition. Price, $5. Pp. 366, with 171 illustrations. Philadelphia: Lea & Febiger, 1946.

The third edition of this book, like the others, presents to students and clinicians a readable and helpful presentation of the clinical aspects of diseases of the blood. It has been rewritten in part and now includes a section on the technic of bone marrow puncture and a description of the findings. It continues to be a most helpful clinical text.

Methods of Diagnosis. By Logan Clendening, M.D., and E. H. Hashinger, M.D. Price, $12.50. Pp. 868, with 143 illustrations. St. Louis: The C. V. Mosby Company, 1947.

Dr. Logan Clendening was a talented physician. Among other gifts he had an ability to express his ideas in writing picturesquely, entertainingly and with great vividness. He must have done his full share in the preparation of this book, for his personality and literary style are impressed on many of its pages.

The volume is divided into two distinct parts. The first deals with methods of clinical diagnosis and the second with laboratory and other special procedures.

The latter part is fairly orthodox and is a well balanced text which meets ordinary standards. The first part is more interesting because here Dr. Clendening's personal touches are so apparent. He attempts to tell any medical student or physician how to make a diagnosis: first by analysis of what the patient says, next by physical examination—and its proper technic is described carefully—and finally by the correct interpretation of what the laboratory may reveal. Fitted into this general pattern to give it color are bits of medical history, anecdotes, a great deal of common sense and a lot of clinical information based on experience. On the whole, therefore, one is likely to read the chapters in this part of the book not only for the information which they contain but also because their perusal is an enjoyable experience in medical literature.

The illustrations, in part diagrammatic and in part photographic, are excellent. The words "I" and "my" appear frequently, and many statements are dogmatic. This introduces a personal element which is not unpleasant; one feels as if Dr. Clendening had prepared each chapter for one's special benefit.

Here is an unusual textbook. Only a rare reader will find it tedious.

gold compounds

in rheumatoid arthritis

results in 6,467 cases

Author	Number of Cases	Per Cent Completely or Greatly Improved	Per Cent Moderately Improved
Forestier (1935)	550	75.0	
Hartfall, Garland and Goldie (1937)	690	66.7	13.0
Sashin, Spanbock and Kling (1939)	80	43.7	38.75
Goldie (1939)	400	76.0	10.5
Logefeil and Hoffman (1941)	139	56.8	24.5
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Cecil, Kammerer and De Prume (1942)	235	66.0	20.0
Price and Leichtentritt (1943)	101	60.0	
Hartung (1943)	264	54.0	
Graham and Fletcher (1943)	95	67.0	20.0
Rawls, Gruskin, Ressa, Dworzan and Schreiber (1944)	100	53.0	21.0
Cohen, Goldman and Dubbs (1945)	259	64.0	
Oren (1946)	250	84.5	
Ragan and Tyson (1946)	142	50.0	39.0
Rose (1947)	91	73.0	11.0
Gardner (1941)	250	40.0	40.0
Robinson (1944)	200	50.0	
Sundelin (1948)	2,441	90.0	
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Complete references in "Present Status of Chrysotherapy in Rheumatoid Arthritis" published by the medical department of G. D. Searle & Co. Copy on request.

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1. Council on Pharmacy and Chemistry: New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Company, 1948, p. 523.
2. Freyberg, R. H., Block, W. D., and Levey, S.: Metabolism, Toxicity and Manner of Action of Gold Compounds Used in the Treatment of Arthritis: I. Human Plasma and Synovial Fluid Concentration and Urinary Thiomalate, Gold Thiosulfate, and Colloidal Gold Sulfide, J. Clin. Investigation 20:401 (July) 1941.

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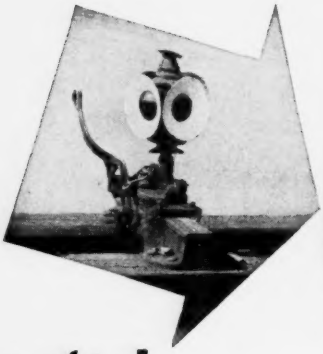

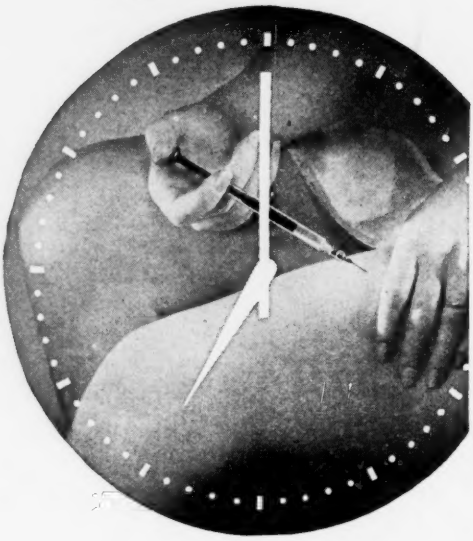

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